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# ANNALS OF INTERNAL MEDICINE

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*Deceased

# A Note on the Composition of Human Sweat*†

RALPH PEMBERTON, M.D., F. A. CAJORI, Ph.D. *and* C. Y. CROUTER, M.S.,
*Philadelphia, Pa.*

INCREASING attention is being devoted to the general field of physiotherapy in the treatment of disease. One of the oldest and most valuable measures in this field is exposure of a part or all of the body to external heat. A conspicuous consequence of this form of treatment is the sweating which is induced. This is so striking a phenomenon as to have led in many quarters to the supposition that toxic material of various kinds may be eliminated in this way. In view of the importance of the sweating process as a therapeutic measure and in view of the relative paucity of precise data bearing upon it, it becomes important to ascertain, if possible, what actually occurs.

For a number of years the physiological effect of external heat, therapeutically applied, has been the subject of investigation in this laboratory. During the course of these studies, considerable data has accumulated relative to the composition of human sweat. The chemistry of sweat in health and diseased conditions, particularly in various skin disorders, has attracted the attention recently of a number of investigators and it seems desirable to make available our existing data, fragmentary though some of it is. This conclusion is further strengthened by the improbability that the present experiments can be carried to completion in the near future by the present workers. These data, which have not been published before have to do, in part, with the reaction of sweat under various conditions and from various parts of the body and with an endeavor to ascertain the factors involved in its reaction. Some figures are available relative to the reaction and to the nitrogen and chloride content of sweat in arthritis, nephritis, scleroderma and psoriasis.

*From the Laboratory of Clinical Chemistry, Presbyterian Hospital.

†The work here reported is part of a study on chronic arthritis in collaboration with R. B. Osgood, M.D., of Boston. The expenses were defrayed by contributions from various sources, including a number of patients.

## REACTION OF SWEAT

Sweat as collected may be either acid or alkaline, the range of reaction being about the range which has been observed for urine, namely, pH 4.8 to 8.4. As has been pointed out before by Pemberton and Crouter (1), the initial sweat is usually more acid than that which is secreted later, if conditions favorable for sweating are maintained. This change in reaction seems to be a compensatory measure to the systemic alkalosis which de-

velops during a "bake," hot bath or other systemic exposure of the body to external heat. (2).

It is questionable whether the true reaction of sweat as it is secreted can be measured in samples collected from the surface of the skin. Upon secretion, sweat is exposed to the air and possible loss of $CO_2$ and other volatile constituents, which may, in part, determine its reaction, may occur. It is well known that $CO_2$ is given off from the skin in appreciable amounts during sweating. The reaction of sweat and its $CO_2$ content has been investigated to some extent by Kittsteiner (3) and Talbert (4).

In order to evaluate the rôle of $CO_2$ in the reaction of sweat, the total $CO_2$ content has been determined in sweat samples, and the effect on the reaction of the removal of $CO_2$ by aeration and boiling has been studied. For this purpose, sweat was collected in a rubber bag that fitted over the hand and forearm of the subject. With the aid of adhesive plaster the bag was tightly sealed around the arm above the elbow. The bag was provided with an outlet tube and the sweat when collected, was allowed to flow through this tube, under oil, into a receptacle. The arm and hand were cleaned with alcohol and ether before being inserted into the bag. The sweat so collected will be referred to as "bag sweat." Sweat from other parts of the body was taken up from cleansed areas in blood-counting pipettes. The pH of the sweat was determined by Felton's spot method (5). This method was of advantage in this work in that it could be carried out on very small amounts of material. It can not be claimed that results obtained in this way are highly accurate ($\pm$ 0.1 pH unit), but in the case of sweat, the results of more accurate analytical determinations would probably be of little significance for the reasons already mentioned. Total $CO_2$ was determined in the Van Slyke apparatus.

The total $CO_2$ content of sweat was found to be very low, even in the more alkaline sweats and, as will be seen from the results in Table I, rarely ex-

TABLE I.

Total $CO_2$ Content of "Bag" Sweat

| No. | pH | $CO_2$ vols. per cent | | No. | pH | $CO_2$ vols. per cent | | No. | pH | $CO_2$ vols. per cent |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4.8 | 0.9 | | 15 | 6.2 | 1.0 | | 43 | 7.0 | 2.3 |
| 6 | 4.8 | 0.5 | | 26 | 6.4 | 0.9 | | 34 | 7.0 | 3.0 |
| 8 | 5.2 | 0.8 | | 39 | 6.4 | 0.2 | | 35 | 7.2 | 4.1 |
| 10 | 5.3 | 3.6 | | 41 | 6.4 | 0.6 | | 37 | 7.2 | 1.8 |
| 40 | 5.6 | 0.2 | | 44 | 6.4 | 0.8 | | 45 | 7.2 | 1.5 |
| 11 | 5.8 | 3.7 | | 23 | 6.6 | 1.4 | | 46 | 7.2 | 2.8 |
| 22 | 6.1 | 0.7 | | 24 | 6.6 | 2.5 | | 42 | 7.4 | 4.7 |
| 14 | 6.2 | 2.3 | | 33 | 7.0 | 5.6 | | | | |

ceeds 4 volumes per cent. The more acid sweats (pH 4.8 to 6.4) in general contain much less $CO_2$ than those whose pH is higher. Since many sweats contain mere traces of $CO_2$, the reaction of sweat would seem frequently to be due to constituents other than carbonic acid or bicarbonates. Carbon dioxide may, however, influence a sweat reaction as is clearly shown by the change in pH that follows the removal of $CO_2$ from an alkaline sweat of comparatively high $CO^2$ content. Also, sweat collected in a rubber bag surrounding the arm and therein exposed to a $CO_2$ tension of the order of 3 to 8 mm. of mercury, was more acid than sweat collected simultaneously from the other arm (Table III).

The effect on the reaction of bag sweat of driving off the $CO_2$ which it contained was investigated. Sweat samples were boiled half a minute or aerated for half an hour with a rapid stream of air. The effect on the pH of allowing sweat to stand several hours was also studied. The results of these observations are given in Table II. Very little change in pH was observed in those sweats with an initial acid reaction. after the removal of $CO_2$. Other sweat samples, with a higher pH and presumably a higher $CO_2$ content, became decidedly more alkaline after boiling and aeration. Exposure to room air had little or no effect on the reaction of the sweat. In our series it was not infrequently observed that after boiling, a sweat

TABLE II

Effect of Boiling, Aeration and Contact with Air on the pH of "Bag" Sweat

| No. | Initial pH | After Boiling pH | After Aeration pH | After Contact with air pH | No. | Initial pH | After Boiling pH | After Aeration pH | After Contact with air pH |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 4.8 | 4.8 | 4.8 | 4.8 | 39 | 6.4 | 6.4 | 6.4 | — |
| 3 | 4.8 | 4.8 | 4.8 | — | 41 | 6.4 | 6.4 | 6.4 | — |
| 6 | 4.8 | 4.8 | 4.8 | — | 20 | 6.6 | 6.6 | 7.1 | 6.6 |
| 4 | 5.0 | 5.0 | — | — | 21 | 6.6 | 6.4 | 7.0 | — |
| 7 | 5.2 | 5.0 | 5.0 | 5.0 | 25 | 6.8 | 7.0 | — | 6.8 |
| 8 | 5.2 | 5.2 | 5.2 | — | 26 | 6.8 | 6.6 | 7.0 | 6.9 |
| 9 | 5.6 | 5.8 | 5.8 | — | 28 | 7.0 | 7.2 | — | 7.0 |
| 40 | 5.6 | 5.6 | 5.6 | 5.6 | 29 | 7.0 | 7.4 | — | 7.0 |
| 12 | 6.0 | 6.0 | — | 6.0 | 30 | 7.0 | 7.0 | — | 7.0 |
| 13 | 6.0 | 7.7 | 7.4 | — | 31 | 7.0 | 6.6 | 8.0 | 7.3 |
| 16 | 6.4 | 6.2 | 6.4 | — | 32 | 7.0 | 8.0 | — | 7.4 |
| 17 | 6.4 | 6.0 | 6.4 | — | 33* | 7.0 | 8.2 | — | — |
| 18 | 6.4 | 6.4 | — | 6.4 | 36 | 7.2 | 8.0 | 7.8 | — |
| 19 | 6.4 | 6.3 | — | 6.4 | 37 | 7.2 | 7.2 | — | — |
| 38 | 6.4 | 6.4 | 6.4 | 6.4 | | | | | |

*Initial $CO_2$ content, 5.6 vols. per cent. After boiling, 0.8 vols. per cent.

sample was slightly more acid than it was before it was boiled. Kittsteiner observed the same phenomenon when he boiled sweat. This increase in acidity was not observed during aeration and consequently it would seem to result from the formation, during heating, of some product acid in nature, rather than to the loss of a volatile base.

Since acid sweat contains only very small amounts of $CO_2$, the alkaline swing observed during sweating is probably the result of an increased elimination in the sweat of basic substances. This bears out the conclusion that the alkalosis observed during the exposure to heat is caused by loss of $CO_2$ by the body, which is partly compensated by excretion of base. (2). Analysis of sweat for total base at intervals during sweating does not always reveal this relation however, for the analytical results must be expressed in per cent composition, and it has been shown that a dilution of sweat occurs during continued sweating (6). This dilution factor may mask the actual increase of base being excreted. In Table III are a few results on total base determinations in sweat, made by Fisk's method (7). No correlation can be seen between the pH and the *per cent* of total base present.

In Table III are also given a few determinations of the fat and fatty acid content of sweat from cleansed areas. It had been noted that certain persons whose skin was distinctly greasy in appearance and feel yielded an acid sweat (forehead sweat pH 4.8). This obviously suggested that fatty acids might be the cause of the low pH. Accordingly some fatty acid determinations were carried out on sweat. Bloor's nephelometric method

TABLE III

Fat and Fatty Acid Content of Sweat and Total Bases in Sweat

| No. | pH | Fat + Fatty Acids mgs. per 100 cc. | | No. | Initial sweat sample | | Sweat sample later | |
|---|---|---|---|---|---|---|---|---|
| | | | | | pH | Total Bases mgs. per 100 cc. | pH | Total Bases mgs. per 100 cc. |
| 1 | 5.4 | 103 | | 1 | 5.5 | 64 | — | — |
| 2 | 5.6 | 14 | | 2 | 5.8 | 82 | 6.2 | 70 |
| 3 | 5.6 | 66 | | 3 | 6.0 | 82 | 6.8 | 50 |
| 4 | 5.8 | 216 | | 4 | 6.2 | 50 | 7.0 | 75 |
| 5 | 6.4 | 184 | | 5 | 6.6 | 39 | — | — |
| 6* | 6.7 | 25 | | 6 | 6.6 | 59 | 7.0 | 54 |
| 7 | 6.8 | 20 | | 7** | 6.6 | 47 | 7.0 | 60 |
| 8 | 6.8 | 83 | | 8 | 6.8 | 68 | — | — |
| 9 | 7.0 | 26 | | | | | | |
| 10 | 7.2 | 72 | | | | | | |
| 11 | 7.4 | 134 | | | | | | |

*Scleroderma **Psoriasis

for blood was used (8), modified to meet the much smaller quantities of fatty acids present in sweat. The proportion of sweat to the alcohol-ether extraction fluid was made larger (1 to 10) than Bloor directed for blood, and weaker standards (0.4 to 2.0 mgs.) were employed for the nephelometric comparisons. It was found that different sweats varied widely in their content of fatty materials. The results, which are expressed as milligrams of fatty acid per 100 cc of sweat, show no correlation between the reaction of the sweat and the quantity of total fatty acids present. There is no indication in these figures that fatty acids are concerned in the reaction of sweat.

A few observations have been made of the inorganic phosphate content of sweat, determined colorimetrically by the method of Benedict and Theis (9). Standards of suitable concentration were employed so as to match the very small quantities of phosphoric acid encountered in sweat. The inorganic phosphorus content of sweat was found to be about 0.1 to 0.3 mg. per cent. There are not sufficient data from which to draw conclusions but no correlation between pH and inorganic phosphorus was suggested from the results that were obtained. The uncertainty of quantitative measurement of such small amounts of phosphorus and the unknown dilution factor of the sweat make it extremely hazardous at present to ascribe the acidity of sweat to the salts of phosphoric acid, or to any other sweat constituent that has been investigated.

Kittsteiner (4), Talbert (5) and others have noted differences in the reaction of sweat at different sites of the body. In Table IV are recorded a few observations of the reaction of sweat secreted simultaneously from different parts of the body and taken up from cleansed areas into blood pipettes. Sweat from the forehead was found almost invariably to be more alkaline than sweat from other sites. Sweat collected from the lower part of the arm and hand was usually more alkaline than that taken from an area over the biceps muscle, though the differences in pH are small and are much less than the differences between the arm sweat and the forehead sweat. There is, however, some suggestion of an influence on the sweat from underlying muscle tissue. Very little difference in pH was found between the lower part of the arm and the lower part of the leg. A more acid sweat was usually encountered in the bag surrounding the arm. In the bag, sweat was exposed to a higher tension of $CO_2$ than was sweat from the corresponding part of the other arm, which was free in the air.

### Sweat in Arthritis

The reaction, lactic acid and total organic acid content, total solids and ash of sweat in chronic arthritis have been reported previously by Cajori, Pemberton and Crouter (2), (6). In respect to these constituents no outstanding differences were detectable between the sweat of the arthritic and that of normal persons. To the above may now be added information on the total nitrogen and sodium chloride in arthritic sweat. Here again the results (Table V) are essentially the same as have been reported for normal sweat.

TABLE IV
PH of Sweat at different Sites on the Body

| No. | Fore-Head (final) | Bag | Lower part free arm | Biceps | Hand | No. | Fore-head (final) | Bag | Lower part free arm | Hand | Lower part leg |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | 8.2 | 7.0 | 8.2 | 7.4 | | 29 | 8.6 | 7.2 | 8.4 | 8.2 | |
| 10 | 8.2 | 7.0 | 7.6 | 7.5 | | 31 | 7.8 | 7.0 | 7.3 | 7.2 | |
| 11 | 8.4 | 6.9 | 7.4 | 7.3 | | 32 | 8.4 | 7.4 | 8.0 | 7.6 | |
| 12 | 8.4 | 7.0 | 7.8 | 7.6 | | 33 | 7.2 | 6.2 | 5.6 | 5.6 | |
| 13 | 8.2 | 7.0 | 7.4 | 7.1 | | 34 | 8.4 | 7.2 | 7.8 | 7.4 | |
| 15 | 7.0 | 6.4 | 6.6 | 6.0 | | 35 | 5.8 | 6.5 | 5.6 | 5.8 | |
| 18 | 7.8 | 6.8 | 7.2 | 6.5 | | 37 | 5.4 | 5.8 | 4.8 | 4.9 | |
| 19 | 8.4 | 6.8 | 8.4 | 7.2 | | 38 | 5.4 | 6.5 | 5.0 | 5.4 | |
| 22 | 8.2 | 6.6 | 7.1 | 6.8 | | 7 | 7.2 | 6.2 | | 7.6 | |
| 23 | 8.1 | 6.4 | 7.9 | 7.3 | | 17 | 8.2 | 6.8 | | 7.2 | |
| 24 | 8.0 | 7.0 | 7.5 | 7.6 | | 30 | 8.2 | 6.6 | | 7.2 | |
| 27 | 8.6 | 7.2 | 8.4 | 8.6 | | 39 | 7.8 | 6.4 | | 7.2 | |
| 20 | 7.8 | 6.2 | 6.8 | 6.5 | | 8 | 7.4 | 6.0 | 6.2 | | |
| 16 | 8.0 | 7.4 | 8.0 | | 8.2 | 21 | 7.1 | 6.2 | 6.4 | | |
| 25 | 8.4 | 7.0 | 7.6 | | 7.4 | 36 | 4.8 | 5.3 | 4.6 | | |
| 26 | 7.0 | 6.0 | 6.2 | | 6.6 | 14 | 8.0 | 6.2 | 6.8 | | |
| 28 | 8.0 | 6.6 | 7.8 | | 6.6 | 40 | 6.8 | | 5.6 | | 5.8 |
| | | | | | | 41 | 7.6 | 7.2 | 7.4 | | 7.2 |
| | | | | | | 42 | 7.0 | 5.4 | 6.0 | | 5.8 |
| | | | | | | 43 | 5.0 | 5.6 | 5.6 | | 5.6 |

TABLE V
Sweat in Arthritis

| Bag Sweat pH | Total N mgs. per 100 cc. | Bag Sweat pH | Total N mgs. per 100 cc. | Bag Sweat pH | NaCl mgs. per 100 cc. | Bag Sweat pH | NaCl mgs. per 100 cc. |
|---|---|---|---|---|---|---|---|
| 7.0 | 65 | 5.4 | 102 | 6.6 | 150 | 6.0 | 220 |
| 5.6 | 76 | — | 108 | 4.8 | 150 | 6.8 | 220 |
| 6.2 | 77 | — | 131 | 6.0 | 160 | 6.0 | 230 |
| 6.8 | 79 | 7.4 | 165 | 6.4 | 160 | 6.8 | 250 |
| 6.4 | 80 | 6.4 | 197 | 6.8 | 200 | 6.8 | 330 |
| 7.2 | 84 | 5.6 | 232 | 6.8 | 210 | | |
| 5.8 | 92 | 6.1 | 241 | 6.4 | 220 | | |

The NaCl and total N agree with the results on normal sweat reported by Berry (10), Riggs (11) and Plaggemeyer and Marshall (12). The results for sweat chlorides, here reported, are below the plateau level found by Adolph (13) and the nitrogen figures are slightly higher than those recently published by Talbert, Silvers and Johnson (14).

### Sweat in Nephritis

A few analyses of sweat collected during therapeutic "bakes" of nephritics are given in Table VI. In common with the experience of others (11), high total nitrogen was encountered in a number of the cases. It is of great clinical importance to know definitely to what extent the sweat glands in nephritis may serve as real aids in the elimination of "toxic" material. The value of sweating measures is accepted in the treatment of nephritis accompanied by edema but various workers (12), (15) doubt that vicarious removal of nitrogenous products takes place through the skin when kidney function is impared. The finding of a high concentration of nitrogen in nephritic sweat points to the possibility, however, that sweat may serve as a valuable vehicle for excretion of nitrogenous substances in this condition. Further work will be necessary before a final explanation of all the benefits that accrue from sweating is forthcoming.

In a somewhat parallel connection it is of interest to ascertain whether in cases of nephritis accompanied by acidosis, the acidosis expresses itself is terms of an acid sweat. It is accepted that acidosis constitutes a part of the pathological picture in some cases of nephritis. Observations were therefore carried out on one case of nephritis which was definitely acidotic and, in addition, on three cases with edema and on four others with nitrogen retention. The range of pH was found to be about the same as that encountered in normal sweat and there

Table VI

Sweat in Nephritis

| No. | Forehead sweat pH | Bag sweat pH | Total N mgs. per 100 cc. | B.U.N. mgs. per 100 cc. | No. | Forehead sweat pH | Bag sweat pH | Total N mgs. per 100 cc. | B.U.N. mgs. per 100 cc. |
|---|---|---|---|---|---|---|---|---|---|
| 3* | 4.8 | 4.8 | — | — | 8 | 7.8 | — | 256 | 55 |
| 4* | 4.8 | 4.8 | — | — | 1** | 8.0 | — | 517 | — |
| 5 | 5.0 | 4.8 | 288 | — | 9*** | 8.0 | 7.4 | — | — |
| 10 | 6.2 | 6.0 | 84 | 22 | 7 | — | 6.6 | 482 | 90 |
| 2* | 7.4 | 6.5 | 262 | 117 | 11 | — | 7.0 | 108 | — |
| 6 | 7.6 | 5.0 | — | 45 | | | | | |

*edema

**Hemorrhagic nephritis

***edema, Plasma pH 7.21

was, therefore, no suggestion that nephritic acidosis induces an acid sweat. The bag sweat of case No. 9 (blood plasma pH 7.21) had a pH of 7.4 and the forehead sweat had a pH of 8.0.

### Sweat in Scleroderma and Psoriasis

The observations in Tables VII and VIII are on the sweat collected from cases of two skin diseases that seem to have something in common, pathologically, with arthritis.

The number of cases studied does not justify much emphasis but in the few observations that have been made there is no indication of deviation from normal in the reaction of sweat in either scleroderma or psoriasis, though in subject "T" (scleroderma) the initial forehead sweat, collected at the beginning of sweating, was distinctly acid, pH 4.8 and pH 5.3. In psoriasis it was quite noticeable that no sweating occurred on the site of the active skin lesion, irrespective of the presence of absence of scales. This was ob-

Table VII
Sweat in Scleroderma

| Subject | Date | Forehead Sweat | | Bag Sweat pH | Total N mgs. per 100 cc. | |
|---|---|---|---|---|---|---|
| | | Initial pH | Final pH | | | |
| T. | 2/9 | 4.8 | 6.8 | 5.6 | 295 | |
| T. | 2/12 | 5.2 | 6.0 | 5.6 | 292 | |
| T. | 2/15 | 5.3 | 6.4 | 6.0 | 178 | |
| T. | 2/27 | 4.8 | 5.8 | 5.0 | 224 | |
| T. | 3/22 | 4.8 | 7.0 | 5.4 | 143 | improved |
| B. | | 8.0 | 8.4 | 6.7 | 140 | |
| M. | | 7.8 | 7.8 | 7.0 | 133 | |
| K. | | | | 6.4 | 101 | |

Table VIII
Sweat in Psoriasis

| No. | Site | Unaffected healthy areas pH | Partly healed areas pH | Total N mgs. per 100 cc. |
|---|---|---|---|---|
| 1 | forehead | 6.8 | 6.8 | 50 |
| 2 | forehead | 7.3 | 5.8 | 82 |
| 3 | forehead | 7.5 | 7.0 | 66 |
| 4 | forehead | 7.0 | 6.4 | |
| 5 | forehead | 7.4 | 7.6 | |
| 6 | abdomen | 7.6 | 6.8 | |

served repeatedly on every case examined. Psoriatic patches that were partly healed showed less active sweat secretion than did clear skin areas. In several cases the sweat collected from partly healed areas was more acid than sweat from uninvolved neighboring areas. Barney (16) found the concentration of the non-protein nitrogen and the sodium chloride in the sweat of psoriatics to be the same as in the sweat of normal persons. In one case of scleroderma observed by us over a period of several months, the sweat nitrogen, high at first, progressively decreased coincident with clinical improvement. In three other cases of scleroderma the content of nitrogen in sweat was not found to be conspicuously high.

## Summary

The total carbon dioxide content of sweat has been determined and the effect of its removal by aeration and boiling on the reaction of sweat has been studied.

Acid sweats were found to contain only very small amounts of $CO_2$ and their reaction was usually not affected by boiling or aerating the sweat. Such sweats appear to be acid because of some component other than $CO_2$. Alkaline sweats contain more $CO_2$. Endeavors to relate the reaction of sweat to its content of fatty acids or phosphoric acid were not successful. The cause of the acidity of sweat remains to be determined. The change in reaction of sweat during long continued sweating, as during therapeutic body bakes, etc., seems to be the result of actual excretion of alkaline substances.

The nitrogen and chloride content of arthritic sweat was not found to be different from the data available in these respects for normal sweat.

The sweat from a few cases of nephritis was examined. In the majority of these an abnormally high nitrogen was encountered. In spite of the doubt of some workers that vicarious elimination of nitrogenous substances takes place through the skin, these figures suggest the possibility that in nephritis the skin may serve as a valuable path for the excretion of nitrogenous substances. The reaction was similar to that found in other persons.

In psoriasis, no sweating appeared over the involved areas and the amount on partly healed areas was less than that on nearby clear skin areas. The reaction and nitrogen content of psoriatic sweat showed no abnormalities. It was observed that the sweat from partly healed areas frequently was more acid than sweat from areas unaffected with psoriasis.

## References

(1) Pemberton, R. and Crouter, C. Y.: J. Am. Med. Ass., 80, 289, (Feb. 3,) 1923.

(2) Cajori, F. A., Crouter, C. Y. and Pemberton, R.: J. Biol. Chem., 57: 217, (Aug.) 1923.

(3) Kittsteiner, C.: Arch. f. Hyg. 73: 275, 1911.

(4) Talbert, G. A.: Am. P. Physiol. 61: 493, (Aug.) 1922.

(5) Felton, L. D.: J. Biol. Chem. 46: 299, (Apr.) 1921.

(6) Cajori, F. A., Crouter, C. Y. and Pemberton, R.: Arch. Int. Med., 34: 566, (Oct.) 1924.
(7) Fisk, C. H.: J. Biol. Chem. 51: 55, (Mar.) 1922.
(8) Bloor, W. R., Pelkan, K. F. and Allen, D. M.: J. Biol. Chem., 52: 191, (May) 1922.
(9) Benedict, S. R. and Theis, R. C.: J. Biol. Chem. 61: 63 (Aug.) 1924.
(10) Berry, E.: Biochem. Zeit., 72: 285, 1915-16.
(11) Riggs, L. D.: J. Exper. Med. 19: 285, 1911.
(12) Plaggemeyer, H. W. and Marshall, E. K.: Arch. Int. Med., 13: 159, (Jan.) 1914.
(13) Adolph, E. F.: Am. J. Physiol. 66: 445, (Nov.) 1923.
(14) Talbert, G. A., Silvers, S. and Johnson, W.: Am. J. Physiol., 81: 81, (June) 1927.
(15) von Noorden, quoted by Matill in Barker: Endocrinology and Metabolism, 3: 867, 1922.
(16) Barney, R. E.: J. Am. Med. Ass., 85: 1373, (Oct. 31) 1925.

# Sclerosis of the Coronary Arteries of the Heart

By Donald L. MacLean, M.B., B.Sc.(Med.), *Department of Pathology, University of Toronto*

INASMUCH as arteriosclerosis itself forms one of the important problems for investigation for both the clinician and pathologist it would seem that any further investigations made with the object of observing in more detail all changes found in the vessel walls would always be opportune. For the present study our observations have been directed toward the coronary arteries of the heart. Our object was to determine how many different types of sclerosis occur in the coronary system; the nature and distribution of these types of sclerosis; and the effect of certain diseases upon the frequency of occurrence of coronary sclerosis.

The material used consisted of a series of unselected hearts from individuals of all ages who came to necropsy in the Toronto General Hospital during the term 1925 to 1926. Ninety-five hearts were thus collected and studied. Gross descriptions were made of the condition of the coronaries and their branches. Sections for microscopic study were then made from the main stems of both coronaries, from the distal portions of both circumflex branches, and from the terminal portions of the anterior descending branches of both circumflex arteries. The muscular branches were studied in sections of the anterior papillary muscle of the left ventricle, and from portions of heart attached to the sections of the descending branches. In certain cases other portions of the coronary system were carefully sectioned as well; particularly where, either from the clinical history or gross findings changes were suspected in certain other areas. The blocks were fixed in 10 percent formalin and embedded in paraffin before cutting with the microtome. Staining was done as a routine by two methods: (a) Haematoxylin and Eosin, and (b) Weigert's Haematoxylin for the elastic tissue. In certain cases Zenker-fixed material was used and sections cut from these were stained by Mallory's phosphotungstic acid haematoxylin or Van Gieson's stains. In selected cases some sections were cut with the freezing microtome and stained with sudan iii and haematoxylin to demonstrate fatty changes. This study was correlated further by keeping an accurate record of the arteriosclerotic changes found elsewhere in the body. Records were kept of the clinical signs and symptoms leading to a diagnosis in each case, together with the age, sex, habits, past illnesses, and the blood pressure findings. It was only in this way we could gauge the

true importance of any pathological findings observed.

The term "arteriosclerosis" as Klotz has often pointed out should include any hardening or thickening of the vessel wall. This has the advantage of allowing the clinician to use the same term rather widely for a variety of conditions which frequently the pathologist alone is able to analyze accurately. Under such a term, then, one may include proliferative as well as degenerative conditions, and often the two are combined.

The anatomy and histology of the coronary arteries has recently received considerable attention from investigators in different countries. The consensus of opinion seems to be that the two coronaries communicate freely through their smaller branches, forming a wide meshwork of arterioles and capillaries. The coronary arteries belong to the muscular type of artery with three coats, the intima, the media, and the adventitia. Before Edholm in 1912 reported his studies little or nothing was written as to the normal histology of the coronary vessels. Faber in the same year published a monograph supplementing Edholm's work, little more appeared until Wolkoff 1923 published his study of nine hearts of different ages. Our work supported the following views: (a) the small muscular arteries of the myocardium and the small epicardial arteries have a similar histological character in normal healthy individuals, i.e. an intima bounded internally by a single layer of endothelial cells and externally by a wavy internal elastic lamina, between which there is only a small amount of fine fibrous tissue. In the intima of the smallest arteries there is no fibrous tissue. The internal elastic lamina as McMeans has pointed out, consists of an acellular band of homogeneous material which under certain conditions will split and disclose its inner composition. This seems to be a laminated structure of fine fibrillar material. McMeans has shown that any inflammatory or toxic substance acting in sufficient concentration results in a dissolution or alteration in the sheath of this elastic lamina and gives the appearance of splitting. Any splitting or alteration of this sort, once induced is permanent, and may be increased by further injury. In these smaller arteries, as a rule, the internal elastic lamina is unbroken and appears as a faintly eosin-staining wavy band encircling the intima either in longitudinal or cross section.

The media, made up of involuntary smooth muscle fibres, varies in its thickness with the diameter of the lumen. Between the muscle fibres which run in a circular direction is a small amount of fine fibrous tissue with few collagen fibres but often showing a small number of fine elastic fibrils. The external coat or adventitia consists of loose connective tissue bundles made up of collagen fibres intermixed with a considerable number of elastic fibrils and some muscle cells. As a rule this coat in the smaller arteries is two or three times the thickness of the media. The elastic tissue rarely forms a true external elastic lamina. In the medium-sized arteries (a group usually constituted by the descending and circumflex branches of the coronaries which run in the epi-

cardial fat), the intima presents a few longitudinal muscle fibres lying internal to the internal elastic lamina.

The main coronary arteries, right and left, constitute the group of larger arteries. Their coats follow roughly the same proportionate sizes to one another as those in the medium-sized group. Small nutrient vessels and sympathetic nerve fibres are nearly always found throughout the adventitia of these main stems. It has not been possible to determine definitely how far inwards these nutrient vessels pass in a normal coronary, but in many cases showing sclerosis these have grown through the wall into the intima. Wolkoff's work gives very good descriptions of the vessels studied, but in the main they showed arteriosclerotic changes. He considered a splitting of the internal elastic lamina, at least in the larger arteries, as a normal condition for a mature artery and went so far as to say that a completely developed intima probably has three layers of elastic and connective tissue in it. We would, on the other hand, insist on the intact internal elastic lamina and the above described characteristic coats as those belonging to a normal artery. Inasmuch as in certain cases also, we have been able to demonstrate arteries from elderly individuals which do not show this complicated type of intima while in others where disease has been or is still acting we have seen it appear at a very early age we do not feel justified in considering all such changes as the normal consequence of age. Jores called a splitting of the elastic lamina and any hypertrophy of the internal longitudinal muscle layer, arteriosclerosis. We, however, would call any thickening of any one of the three coats a type of arteriosclerosis.

*Types of Sclerosis Occurring in the Coronary Vessels.* In our series a great preponderance was found in the frequency of intimal changes, as compared to the sclerosis of the other coats. This held true in all the coronary vessels except the small muscular or finest subepicardial twigs, in which a thickening of the adventitia formed the commoner type of lesion. Chronic nodular or diffuse endarteritis is by far the most common type of sclerosis in the coronaries of the heart. The early changes observed in this lesion seem to consist of one of two things (a) a deposition, layer upon layer, of the endothelial lining, and (b) an increase in the delicate sub-endothelial connective tissue stroma. The latter may be small at first, and may be accompanied by a mild infiltration from the lumen of large mononuclear cells and lymphocytes. At times this connective tissue increase is definitely made up of collagen fibres, while at other times there seems to be a clear, homogeneous material with relatively few fibroblastic cells. This would lead one to suspect that the endothelial cells have laid down some type of matrix. These fibres may show further changes, often becoming swollen, and pale staining, and at other times appearing hyaline. Frequently these areas seem to undergo a bland necrosis, losing their staining ability and appearing as a fine reticulated debris as though all the original substance were gone and only the skeleton of the fibres remained. These areas show practical-

ly no accompanying cellular infiltration. Other areas of the artery, however, show that the cellular infiltration has progressed through the entire depth of the intima. If the individual has suffered a severe purulent infection, it is commonly manifested by increased numbers of polymorphonuclears and other inflammatory cells in the intima itself. Not uncommonly one can make out the signs of an acute endarteritis superimposed upon a chronic endarteritis. In our study of the coronaries we found the presence of vasa vasora in the intima in the more marked cases of nodular endarteritis, and not necessarily related to a syphilitic process. Other changes may and usually do occur as time goes on in the nodular thickening of the intima. One of the first of these is the fatty change so commonly seen. When an undue amount of fat is present within a cell or its fibrillar processes one may speak of it as "fatty degeneration" (Klotz). This often occurs in the collagen fibres of the much thickened intima. When the fat in these cells and in the stroma is freed by destructive processes one is confronted by a different condition. Such a state is spoken of as "atheroma" and is recognized both macroscopically and microscopically as a gruelly mass of fat, protoplasmic detritus and cholesterol crystals. From our study it is probable that every type of cell in the intima may undergo fatty degeneration at one time and another and such an accumulation of fat can be disposed of only by chemical combinations with the tissue fluids. The process of calcification has been investigated by Klotz who states that while soluble compounds of the fatty acids and cholesterol esters may be formed, the insoluble calcium and magnesium soaps occur just as frequently. Calcification then is a stage in the degenerative process. The calcium deposits occurred nearly always in association with atheromatous changes. Associated with these processes fine calcium granules may appear in the hyaline areas of the connective tissue in the intima.

Chronic nodular endarteritis as stated above forms the largest group of sclerotic changes found in the coronaries. In the gross these arteries vary from the barely palpable thickenings, to the group of very tortuous nodularly thickened vessels, almost pipestem in hardness. These may be irregularly hardened, some areas being entirely encircled by a calcareous ring, whilst other areas are not. The case may be conveniently subdivided into (a) chronic nodular or diffuse endarteritis (1) simple, (2) with early fatty degeneration, (3) with hyaline degeneration, (4) with atheroma, (5) with calcification. There of course may be any combination of these present. A discussion of the incidence of these will appear later. In certain cases notably those in which the individual has suffered some acute infection one finds in the gross some delicate yellow streakings in the intima. These may run lengthwise or appear as oval areas. They are seldom palpable. These, if sectioned, preferably with the freezing microtome, show the presence of large, pale, oval or round cells with a foamy vacuolated cytoplasm in the centre of which is a small round nucleus. These cells have been called foam cells and while filled with large

amounts of lipoids and cholesterol esters, still are to be differentiated from atheroma. Large numbers of these cells recuperate and the fatty streaks in the gross tend to disappear. Such fatty change in the coronaries, occurs mainly in the intimal tissues although a few have been observed in the media. Only rarely were these observed in the coronaries apart from a similar condition in the aorta.

*Changes in the Musculo-Elastic Layer.* As mentioned above we do not agree with Wolkoff that a marked change in the musculo-elastic layer is to be considered as a simple age phenomenon. We would draw attention to the fact that the cases described by him were those of septicaemia, scarlet fever, pneumonia, uterine rupture, and fibrino-purulent peritonitis etc. We would expect such cases to show inflammatory changes in the intima or media, and in view of McMean's work, the internal elastic lamina would also probably show longitudinal splitting. We have observed cases of aged individuals whose arteries did not show these changes, and on the other hand, arteries from a fourteen year old child which did show them to a marked degree. The process underlying a hypertrophy of the internal longitudinal muscle layer of the intima is not as yet fully understood. We have observed a marked hypertrophy of this layer at the early age of five days, and at succeeding ages upwards. One notable case seeming to support Jores' theory that hypertension results in a hypertrophy of this layer, was found in an individual of twenty one years (A-184-25) who suffered a condition of congenital absence of the main pulmonary artery. Both ventricles opened into a common aorta, and a pressure of 250 mm. Hg. was found clinically in the right brachial artery. At autopsy the arteries stood out as tortuous and tremendously thickened vessels. On examination we were surprised to find that the thickening was mainly due to a marked hypertrophy of the musculo-elastic layer. Numerous other cases of hypertension were examined in which one was unable to demonstrate a similar change.

As a rule, the changes in the musculo-elastic layer are as follows: the internal elastic lamina splits into two layers which become separated by a few longitudinally running muscle fibres, a small amount of connective tissue and occasionally some foam cells. The inner of these two layers, which is called "the grenzelamella" (Jores, Torhorst, Wolkoff), then undergoes further splitting. This results in a layer of irregular circularly disposed strands of elastic tissue. The whole mass lying between the split elastic fibres constitutes the hyperplastic layer of Jores. As the individual advances in years, certain changes seem to occur whereby this hyperplastic layer becomes altered and more difficult to stain until finally very little elastic tissue can be demonstrated in the senile artery. Early changes in the internal elastic lamina may be hard to recognize. As McMeans has pointed out for other arteries, the changes consist of a granular appearance, some swelling, or slight variation in staining qualities. Other changes are easily seen, such as a clumping of the elastin in a granular manner, and a little later calcification of this structure frequent-

ly occurs. It is possible that certain fatty changes may precede this calcification of the lamina. One of our cases aged twenty three years showed this calcification of the internal elastic lamina to a marked degree. This was one of the youngest cases showing calcium deposits in the coronaries and was present in the internal elastic lamina, but not elsewhere in the artery.

*Changes in the Media.* A mesarteritis of the coronary does not occur nearly as frequently as an endarteritis. It may consist simply of an inflammatory reaction so frequently seen accompanying acute systemic infections. In such cases, small aggregations of inflammatory cells, lymphocytes, endothelials, plasma cells, and occasionally some polymorphonuclears are found. These are usually in association with the vasa vasora. Syphilitic or rheumatic mesarteritis as described in the aorta by Klotz, Pappenheimer and Von Glahn are not nearly as easily recognized in the coronaries as in the aorta. Healing of such cases of mesarteritis as does occur is by fibrosis. It is probable that certain cases of severe intoxication result in cloudy swelling and degeneration of the muscle fibres in the media. These too may be replaced by fibrosis. Feytre in 1925 reported a case of myomalacia cordis in which this fibrosis of the media was a marked condition. Schmiedl described a similar condition in the superior mesenteric artery. Usually the fibrosis is more marked on the outer side of the media, as though it were derived from the adventitia. At other times nearly the whole thickness of the media is affected. This type of lesion progresses further along the coronaries, towards the finer ramifications than any other type. Usually there is some slight increase in the elastic fibres too.

Besides this fibrosis one frequently notes a great thinning and atrophy of the media beneath the area of nodular endarteritis. MacCordick studying the radial artery, found medial atrophy in cases of pernicious anemia, and other wasting diseases. In some cases he found hypertrophy and hyperplasia with chronic nephritis and hypertension. Moreover he noted such medial changes without accompanying changes necessarily being present in the intima. Although exact measurements as done by him were beyond the scope of this work, yet some attention was paid to this, with the result that no thinning or atrophy was found apart from the nodular intimal thickening. No localized hypertrophy of the media was found. Thinning of the media may be explained by the fact that an increase in the thickness of the intima reduces the nutrition to the inner part of the media, which derives its supply mainly through diffusion from the lumen. Then the pressure, whether normal or increased, acting on the weakened wall may result in a stretching and gradual thinning as is so frequently noted behind the nodular thickening. No area of calcification or atheroma was observed in the media. No case of medial calcification of the coronaries of the heart was found in the literature, and from our own experience we are safe in concluding that "Moenckeberg's sclerosis," the type so frequently found clinically in the

peripheral vessels, rarely if ever occurs in the arteries of the heart.

*Adventitial Changes.* Adventitial changes in the coronaries, either in the large or small branches are usually inflammatory in nature, and are accompanied by the various inflammatory cells depending on the type and severity of the reaction. In the finest twigs running in the epicardial fat or in the muscular branches, particularly those in the papillary muscles, one may find a marked fibrosis. This may be either the healing or healed stage of a previous inflammatory condition in the adventitia, a type common to the finest branches. This fibrosis of the adventitia invades the media and in this minute type of artery the media may be almost completely replaced by fibrous tissue. As this fibrosis contracts, it tends to narrow the lumen of the arteries and results in nutritional disturbances in the surrounding heart muscle. As the muscle fibres are injured by such vascular changes, they are replaced by new fibrous tissue, the result of which is an increase of the areas of fibrosis in the myocardium. It is probable that the majority of the cases of this type of sclerosis are related to rheumatic fever and syphilis. Thalheimer and Rothschild believe that many of these small fibroses represent healed Aschoff bodies. Nutritional disturbances to the heart muscle likewise may result from arterial changes (nodular endarteritis) in the proximal portion of the left coronary and its anterior descending branch, which are the commonest sites for such a lesion and may account for the greater preponderance of myocardial fibrosis seen in the septum.

*Age Appearance of Sclerosis.* Accepting the definition of arteriosclerosis as laid down in the beginning of this paper, we found sclerosis present at the early age of five days. This case (A-42-26) was that of an infant of normal birth who vomited for five days and died. At autopsy an anomaly of the duodenum was found wherein no connection between it and the jejunum was present. Both the right and left coronary arteries in this case showed a nodular thickening of the intima which proved to be an hypertrophy of the musculo-elastic layer of the intima. This hypertrophy was more marked in the left coronary where the internal elastic lamina was also split. Cases of marked sclerosis were also found at the ages of 14, 16, and 20 years respectively. From then on sclerosis in one or more form to a varying degree was found in nearly every case. The earliest occurrence of calcium deposit was in the internal elastic lamina of the coronary artery, at the age of 23 years. The earliest case of atheroma was aged 23 years. Calcification of the intima did not commonly occur before 50 years. The youngest case in which a definite adventitial fibrosis of the muscular arteries was present was 16 years of age. Cases of arteriosclerosis occurring in early life are not unique (Freemont and Smith, Durant, Meigs, Hodgson, Adler and Wiesner, Bryant and White).

Analysis of Table I shows that the frequency of arterial changes in the coronaries of the heart increases with age up to 50 years after which practically every one shows some sclerosis of the coronary arteries. Moreover

TABLE I

| Age periods of cases studied | Years 1-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | over 71 |
|---|---|---|---|---|---|---|---|
| Number of cases studied | 14 | 6 | 15 | 16 | 18 | 17 | 9 |
| Coronary sclerosis (all grades) | 4 | 3 | 10 | 12 | 17 | 17 | 9 |
| Fibrosis of adventitia | 3 | 2 | 8 | 5 | 10 | 8 | 6 |
| Atheroma | 0 | 1 | 4 | 6 | 11 | 13 | 6 |
| Calcification | 0 | 1 | 1 | 3 | 10 | 10 | 5 |
| Sudden death | 0 | 0 | 1 | 1 | 4 | 3 | 3 |
| High Blood pressure | 0 | 1 | 1 | 3 | 4 | 5 | 3 |
| Hypertrophy of the musculo-elastic layer | 2 | 2 | 0 | 1 | 3 | 2 | 0 |
| Medial fibrosis | 1 | 1 | 3 | 3 | 4 | 5 | 4 |
| Percentage of examined cases showing cerebral sclerosis | 0 | 0 | 16 | 50 | 57 | 100 | 100 |

chronic nodular endarteritis is by far the most common lesion observed. Calcification and atheroma appear as the late degenerative changes and are seldom seen under 30 years. Neither of these occurred apart from chronic nodular endarteritis, and atheroma itself occurs slightly more frequently than calcification. Fibrosis of the adventitia in the small arterioles and muscular branches is seen either with or without gross fibrosis in the myocardium. Such a type of lesion rarely is seen under 30 years and progressively increases with age. It is usually associated with endarterial changes in the larger trunks of the coronaries but not necessarily so (Anitschkow, Fischer, Martinotti, Mircoli and Bonome). Inflammatory changes appear to be distributed more or less uniformly along the course of the coronaries and may occur at any age. Seventeen cases with a systolic blood pressure of 150 mm Hg or over were studied but no arterial changes characteristic of increased blood pressure were found. Thirty cases died of some acute illness. These showed recent inflammatory changes in the various coats. It is likely that acute infections as well as rheumatic fever give rise to an increased number of arteriosclerotic cases (Klotz, Thayer and Brush).

*Relation of Sclerosis of the Coronary Arteries to Sclerosis Elsewhere.* Another interesting point is observed in the comparison of the prevalence of coronary sclerosis with the incidence of scleroses elsewhere. Willius and Brown have given us a series of figures which are compared with our own in Table II.

The data obtained by Willius and Brown in the study of coronary sclerosis was analysed from quite a

TABLE II

| | Our series of 95 cases | Willius and Brown's series of 86 cases |
|---|---|---|
| Coronary sclerosis occurred in | 76% | 100% |
| Cerebral sclerosis occurred in | 52% | 86% |
| Aortic sclerosis occurred in | 92% | 99% |
| Valvular changes occurred in | 67% | 51% |
| Lesions of myocardium occurred in | 43% | 100%* |
| Renal sclerosis occurred in | 25% | 37% |
| Peripheral sclerosis occurred in | 22% | 70% |
| Infarcts myocardium occurred in | 2% | 8% |
| Accessory coronary arteries occurred in | 13% | |
| Sudden death due to cardio-vascular causes occurred in | 13% | 37% |

*Willius and Brown include cloudy swelling. segmentation, fragmentation, fatty degenerations, etc., hence their figures are scarcely comparable with ours.

different angle than those of our own. Their series of eighty-six cases were chosen for the study of an obvious coronary sclerosis to obtain the relationship between this lesion and the clinical manifestations in the patient. We, on the other hand, were desirous of determining the manner of development of coronary scleroses of all cases. Hence, apparent discrepancies appear in the comparison of our figures, for as they state in their article, the average age of the patient in their series was sixty years, while ours was in the forties. The increasing incidence of all forms of scleroses in the ascending decades of life is well illustrated in the comparison of the two series of cases.

## SUMMARY

(1) Coronary sclerosis is the second commonest type of arteriosclerosis which we have encountered. It cannot be gauged by examination of the peripheral arteries alone.

(2) The distribution of sclerotic changes in the coronaries of the heart varies widely according to the portion of this arterial system examined. Intimal changes occur most frequently in the main coronaries, less frequently in the larger branches, and are seldom seen in the fine muscular twigs. Adventitial changes on the other hand are more common in the finer muscular branches.

(3) Coronary sclerosis is usually present in both coronaries. It is more marked however, in the left coronary than the right.

(4) Nodular endarteritis is the most common lesion affecting the coronary arteries of the heart, and it often produces marked obstruction to the lumen. It rarely occurs apart from an aortic sclerosis.

(5) Atheroma and calcification of the intima of the coronaries rarely occur in the smaller branches. This lesion increases in frequency with age. and is nearly always secondary to a chronic nodular endarteritis.

(6) Fatty degenerations may occur in any portion of the intima or media.

Fatty streaks in the intima are usually found associated with intoxications, acute infectious diseases and metabolic disturbances.

(7) Calcification of the internal elastic lamina when it occurs, may be the only calcified area in the artery.

(8) Acute systemic infections are evidenced in the coronaries of the heart by cellular reactions in the various coats. As a rule these are more marked in the adventitia and intima than in the media.

(9) The most common lesion in the finer muscular branches and epicardial twigs is an increase in the connective tissue about the adventitia.

(10) Fibrosis of the myocardium is probably largely an end result of coronary disease, especially the fibrosis occurring around the finest vessels which is related to an adventitial type of sclerosis.

(11) The most common site for coronary occlusion is at the commencement of the anterior descending branch of the left coronary. The occlusion is nearly always the result of a process of thrombosis. Nodular endarteritis or atheromatous changes alone rarely, if ever, produce occlusion.

(12) Occlusion of one coronary, if not too suddenly produced, results in so-called "anemic infarcts," which may heal by fibrosis.

(13) The symptom-complex, angina pectoris, is commonly related to coronary sclerosis.

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## REFERENCES

(1) Adler: Experimental Arterial Disease. Amer. Jour. Med. Sci., 1908, 136, 241.

(2) Allbutt: Diseases of the Arteries including Angina Pectoris. Vol. 2, p. 368, London, 1918.

(3) Aschoff: Zur Myocarditisfrage. Verhandl. d. deutsch. path. Gesellsch, 1904, 8, 46.

(4) Aschoff: A Discussion of Some Aspects of Heart Block. Brit. Med. Jour., 1906, 2, 1103.

(5) Aschoff: Entwicklung, Wachstums und Altersvorgange an den Gefassen. Jena, 1908.

(6) Anitschkow: Die Neubildung des Granulationsgewebes im Herzmuskel. Ziegler's Beitrage, 1913, 55, 373.

(7) Benson and Hunter: Pathology of Coronary Artery Disease. Northwest Medicine, Seattle, 1925, 24, 606.

(8) Blumer: Coronary Thrombosis. Albany Med. Ann., 1922. 43, 288.

(9) Bonome: Uber die Heilung der Asept. Herzwunden. Ziegler's Beitrage, 1889, 5, 265.

(10) Bryant and White: A case of Calcification of Arteries in a Child aged Six Months. Guy's Hosp. Reports, 1899, 4, 18.

(11) Christian: Cardiac Infarction. Northwest Medicine, Seattle, 1925, 24, 593.

(12) Cowan: Fatty Degenerations of Myocardium. Jour. of Path. and Bact., 1903, 8, 17.

(13) Edholm: Arteria Coronaria Cordis des Menschen. Anatomischer Anzeiger, 1902, 42.

(14) Faber: Die Arteriosclerose. Jena. 1912.

(15) Feytre: Ein eigenartiger Fall von Myomalacia Cordis. Frankfurter Zeitschr. f. Path., 1925, 33, 1.

(16) Freemont and Smith: Arteriosclerosis in the Young. Amer. Jour. Med. Sci., 1908, 135, 199.

(17) Gibson and Muir: Cardiac Fibrosis as a Result of Coronary Obstruction. Edinburgh Hosp. Reports, 1894, Vol. 2.

(18) Gross: The Blood Supply to the Heart in its Anatomical and Clinical Aspects. New York, Hoeber, 1921.

(19) Hamburger, Priest, Bettman and Howard: Experimental Coronary Embolism. Amer. Jour. Med. Sci., 1926, 171, 168.

(20) Herrick: Thrombosis of Coronary Arteries. Jour. Amer. Med. Asso., 1919, 72, 387.

(21) Jacob: Hyaline Degeneration of Arteries. Jour. Med. Res., 1917, 35, 187.

(22) Jamieson and Hauser: Angina Pectoris in a Youth of Eighteen Years. Jour. Amer. Med. Assoc., 1925, 85, 1398.

(23) Jores: Zur Kentniss d. Regen. und Neubildung elast. Gewebs. Ziegler's Beiträge, 1900, 27, 381.

(24) Jores: Neubildung elastischer Fasern in der Intima. Ziegler's Beiträge, 1898, 24, 458.

(25) Jores: Isolirte Verkalkung d. elast. Interna. Ziegler's Beiträge, 1902, 31, 571.

(26) Jores: Ueber Erkrankungen d. Arterien d. Struma. Ziegler's Beiträge, 1897, 21, 211.

(27) Jores: Wesen und Entwicklung der Arteriosklerose. Wiesbaden, 1903.

(28) Jores: Uber die feiner Bildung u. d. Wiederbildung des elastischen Bindegewebs. Ziegler's Beitrage, 1907, 41, 167.

(29) Klotz: Nodular Endarteritis of the Aorta about the Intercostal Arteries. Jour. Med. Res., 1915, 31, 409.

(30) Klotz: Concerning Compensatory Hyperplasia of the Intima. Jour. Exp. Med., 1910, 12. 707.

(31) Klotz: Studies on Calcareous Degeneration. Jour. Exp. Med., 1905, 7, 633.

(32) Klotz: Studies on Calcareous Degeneration. Jour. Exp. Med., 1906, 8, 322.

(33) Klotz: Arterial Lesions in Rheumatic Fever. Jour. Path. and Bact., 1913, 18, 259.

(34) Klotz: Arteriosclerosis. Can. Med. Assoc. Jour., 1926, 16, 11.

(35) Klotz and McMeans: Superficial Fatty Streaks of Arteries. Jour. Med. Res., 1916, 34, 41.

(36) Klotz and Manning: Fatty Streaks in Intima of Arteries. Jour. Path. and Bact., 1911, 16, 211.

(37) MacCordick: Normal Growth, Atrophy, and Hypertrophy of the Middle Coat of a Radial Artery. Jour. Med. Res., 1914, N.S. 25, 185.

(38) Martinotti: Sugli effetti delle ferite del Cuore. Giorn della Accad. di Med. di Torino, 1888, No. 7 (Cited by Anitschkow).

(39) McMeans: Splitting of the Elastic Fibres in Arteries. Jour. Med. Res., 1915, 32, 377.

(40) McMeans: Occurrence of Arteritis in Meningitis. Jour. Amer. Med. Sci., 1916, 151, 249.

(41) Meigs: Chronic Endarteritis — Its Clinical and Pathological Effects. Trans. Coll. Phys. Phila., 1889, 3S, 11, 159.

(42) Miller and Mathews: Effect on Heart of Experimental Obstruction of Left Coronary. Arch. Int. Med., 1909, 3, 476.

(43) Pappenheimer and Von Glahn: A Case of Rheumatic Aortitis. Amer. Jour. Path., 1926, 2, 1.

(44) Smith: Concerning the Anatomy of Coronary Arteries. Amer. Jour. Med. Sci., 1918, 156, 706.

(45) Smith: Ligation of the Coronary Arteries, etc. Arch. Int. Med., 1918, 22, 8.

(46) Smith: Ligation of the Coronary Arteries. Arch. Int. Med., 1920, 25, 673.

(47) SMITH: Ligation of a Dog's Left Coronary and Electro-cardiographic Changes. Arch. Int. Med., 1922, 32, 497.

(48) THAYER AND FABYAN: Studies on Arteriosclerosis. Amer. Jour. Med. Sci., 1907, 134, 84.

(49) TORHORST: Sklerose der Pulmonalarterien. Ziegler's Beitrage, 1904, 36, 210.

(50) VON GLAHN: Coronary Disease and Infarct of the Heart. Proceed. New York Path. Soc., 1923, N. S. Vol. 23, 1-5.

(51) WERLEY: Cardiac Infarct and Coronary Sclerosis. Texas State Jour. Med., 1925, 21, 428.

(52) WILLIUS AND BROWN: Coronary Sclerosis. Amer. Jour. Med. Sci., 1924, 168, 165.

(53) WIESNER: Uber d. Veränderungen der Koronargefasse bei Infectionskrankheiten. Wien. Klin. Woch., 1906, 19, 725.

(54) WOLKOFF: Uber de. Histolog. Strucktur. d. Coronararterien d. men. Herz. Virch. Archiv. f. Path., 1923, 241, 42.

(55) WOOLLEY: Consequences of Coronary Lesions. Jour. Lab. and Clinic. Med., 1917, 3, 192.

# Gastric Tuberculosis With Report of Two Cases*

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TUBERCULOSIS of the stomach is seldom encountered and practically never diagnosed clinically. Two instances of it are on record at the University of Michigan Hospital. In a series of 2900 consecutive autopsies, one case was encountered. In the routine pathological examination of surgical specimens, another case has recently been found.

Broders of the Mayo Clinic made an exhaustive review and analysis of the literature on the subject in 1917. He reported the single case occurring in their series of 2501 gastric operations. His analysis included 305 published cases, in addition to his own. He divided the cases into four groups, as follows:

1. Positive cases. Those which present an histologic picture of tuberculosis plus the presence of the tubercle bacillus in the depths of the lesion, or the presence of the specific bacillus in the depths of an indefinite histologic lesion.

2. Probable cases. All cases that possess an histologic picture of tuberculosis.

3. Doubtful cases. All those with a good gross description of tuberculosis or a good gross description plus a poor histologic description.

4. Rejected cases. Those that cannot meet the qualifications of the three preceding classes.

It is interesting to note that in only 49, or 16 per cent of the cases analyzed by Broders, were tubercle bacilli demonstrated, establishing what he would call a positive diagnosis. In 118 more cases, or 38.8 per cent of those reviewed the histologic picture was that of tuberculosis. It thus becomes apparent that nearly half the cases reported were to be classified as doubtful or rejected. It was further shown in this analysis that adults were affected more often than children, the ratio being about 3 to 1. Males were affected more often than females, the ratio being 2 to 1. Ulcer was the predominating lesion in the positive and probable cases, constituting 81.6 per cent of the former and 80.5 per cent of the latter. In the positive cases the lesser curvature was the most frequent site of the ulcer or ulcers, and the pylorus the most common site in the probable cases and in a combination of the positive and probable cases. In tuberculosis or other organs associated with gastric tuberculosis, the lungs were most commonly affect-

*From the Department of Pathology, University of Michigan. Service of Dr. Warthin.

ed (69 per cent of positive and 86 per cent of probable cases), closely followed by the intestines (59 per cent of positive and 69 per cent of probable cases). Broders further pointed out that no case of tuberculosis of the stomach had been absolutely proved to be primary in the stomach.

Razzaboni in 1919 reported a case in which subtotal gastrectomy was done on a woman 60 years old, with a typical clinical picture of gastric carcinoma. The greater part of the tumor was on the lesser curvature, but it infiltrated most of the stomach. On the inside of the stomach there was an ulcer crater larger than a dollar, with margins deep, hard and distinct. Microscopical sections showed the typical histologic picture of tuberculosis in the base of the ulcer, some distance from the ulcer and in omental lymph nodes. Tubercle bacilli could not be stained, but fortunately the material was handled in such a manner that it was possible to use some of it for animal inoculation. This showed the lesion to be definitely tuberculous. Razzaboni's patient was apparently in good health three and one half years after operation.

Geuken in 1920 published an account of a patient 35 years old who had had pleurisy two years before the onset of gastric complaints. At operation "a hard string of tuberculous tissue was compressing the stomach in several places, whilst in the forewall of the stomach were to be found tuberculous foci. Four years afterward the patient died of general tuberculosis." The author did not record the histologic examination.

Suermondt in 1925 found after resection of a gastric ulcer that it was an exclusively tuberculous process, with connected cheesy glands. No other manifestations of tuberculosis were discovered elsewhere but roentgenoscopy revealed traces of an apparently healed small tuberculous focus in the right lung.

In 1925 Hurst reported with some detail the case of a man 46 years old with a history of ten years of epigastric pain. There was nearly complete achlorhydria and always occult blood in the stools. X-rays of the chest were suggestive of chronic tuberculous disease. There was no pyrexia and the Wassermann test was negative. X-rays of the stomach showed an irregular ulcer crater suggestive of malignant degeneration. Examination of the lesion after partial gastrectomy revealed what appeared to be a simple ulcer three-fourths of an inch in diameter, a little below the middle of the lesser curvature. Sections showed a tuberculous process occupying the thickened margins of the ulcer and infiltrating the surrounding regions. The tubercles were typical and occurred freely in the mucosa and submucosa, the wall beneath being thickened by fibrous tissue. Hurst concluded that the condition was caused by secondary infection of a chronic gastric ulcer with tubercle bacilli from swallowed sputum. He did not state the results of any search for tubercle bacilli in the lesion.

In 1925 Lundgren showed at autopsy that a dilatation of the esophagus in a man 55 years old, which had been thought to be due to cardiospasm, was the result of a nodular tuberculous

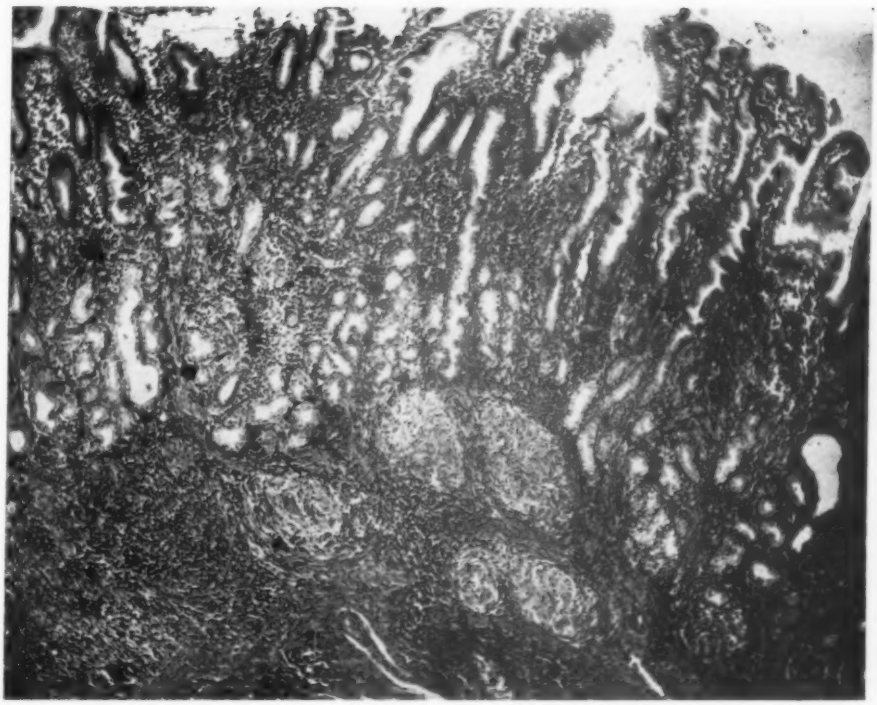

FIG. 1. Low power view of stomach mucosa at border of ulcer, showing a group of miliary tubercles in submucosa, and small one in mucosa.

process of the cardia of the stomach. A good histologic description was presented, but apparently tubercle bacilli were not demonstrated.

Faltin in 1927 demonstrated an adenocarcinoma developing at the border of a large tuberculous ulcer in the stomach of a man 62 years old. The patient had had pulmonary trouble for years, but tubercle bacilli never could be found in the sputum. The lymph glands along the lesser curvature were also tuberculous. Prior to operation marked hyperacidity and disturbed motility of the stomach were demonstrated. The author believed the adenocarcinoma was secondary to the tuberculous ulceration.

Collinson and Stewart in 1928 found tuberculous ulceration of the stomach in only three cases out of a series of 10,000 autopsies at the Leeds Infirmary, and "in two of these it was due to involvement from without by adjacent tuberculous lymph glands. In a series of 320 partial gastrectomies in which the specimens were examined microscopically, none were the seat of tuberculous ulceration, but in two cases a simple chronic ulcer was associated with scattered miliary tubercles throughout the mucosa, while in a third, typical 'carcinoma ex ulcere' coexisted with a lesion at least strongly suggestive of tubercle." The latter case occurred in a man 31 years old. The

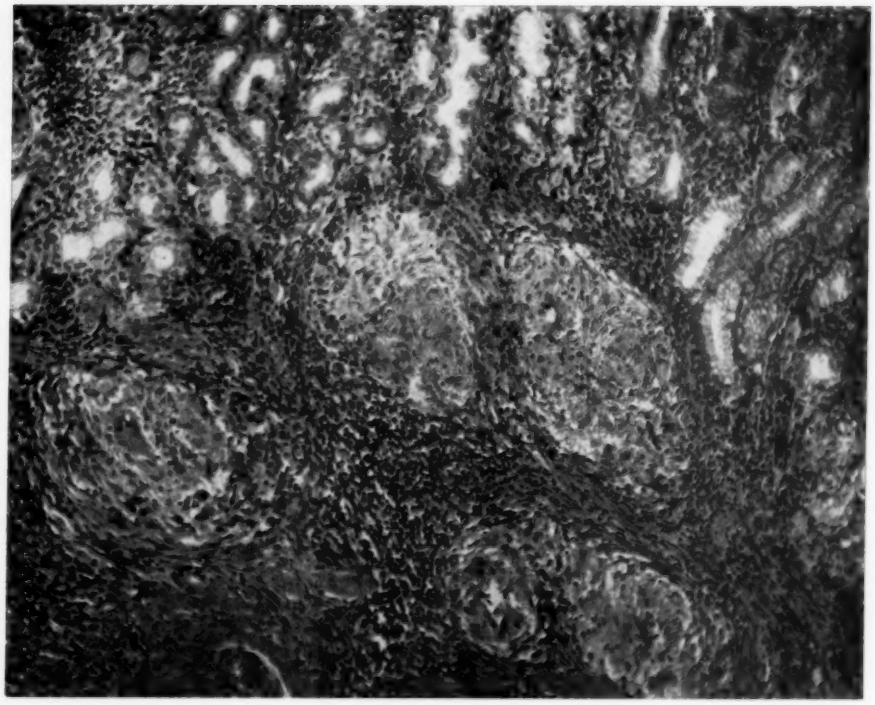

FIG. 2. Higher power view of preceding, showing group of miliary tubercles in mucosa and submucosa.

other two surgical cases were in women aged 57 and 45 years. Excellent histologic evidence was shown of tuberculosis. Prolonged search for tubercle bacilli, however, was futile. The authors showed by their statistics that the type of person who develops a gastric or duodenal ulcer is less commonly the subject of tuberculous infection than the general population.

## ROUTES OF INFECTION AND RELATIVE IMMUNITY

Willerding has summed up the possibilities by which the stomach may become infected with tuberculosis, as follows: (1) hematogenous, (2) lymphogenous, (3) transserosa, (4) from swallowed sputum in pulmonary tuberculosis, (5) by antiperistalsis from tuberculous enteritis.

It has been stated that in order to infect the mucosa a break in the continuity of the mucosa and a decrease in the acidity of the gastric contents are necessary (Duerck). We are fairly willing to grant that the first, that is, a break in the continuity of the mucosa, is necessary. However, the work of Zagari, Strauss and Wuertz, Carrière, and others has shown definitely that the virulence of tubercle bacilli is scarcely affected unless they are in contact with gastric juice for at least twelve hours.

Arloing was unable to produce tuberculous gastric ulcers in animals

when, after introducing human tubercle bacilli into their stomachs through fistulae or mucosal inoculations, he changed the acidity to strongly acid and strongly alkaline, ligated arteries along the greater curvature, and produced ulcerations of the mucosa by the electric needle and mucosal injections of an emetic. In another series he injected tubercle bacilli intravascularly and produced gastric ulcers, which however, were not definitely tuberculous. He did produce two tuberculous duodenal ulcers in dogs by this method, and all of his animals showed polyvisceral miliary lesions. In still another series, by means of interstitial inoculation of the gastric wall, he was occasionally able to produce tuberculous ulceration.

It is interesting to note that in a case reported by Hoppell and Blumer, the patient had advanced pulmonary tuberculosis, chronic gastric ulcers, and an absence of free hydrochloric acid in the gastric contents. Microscopic examination of the ulcers showed tubercle bacilli over the surface, but in the depths of the ulcers there were neither tubercle bacilli nor tubercles.

There has been considerable difficulty in deciding in some cases whether a tuberculous ulceration had been set up opposite adherent tuberculous glands, or whether the adherent glands were infected through the lymphatics from the region of the primary infected ulcer. It seems possible that either of these might occur.

There are several cases on record in which there is little doubt that the gastric wall has been involved through continuity and contiguity of structure. It is not uncommon, at autopsy, in cases of advanced peritoneal tuberculosis, to see the stomach cemented to the liver, spleen, diaphragm, pancreas and intestines by solid caseous material, yet the rarity with which the gastric wall itself is really involved in these cases is remarkable. It is a commonly accepted fact that the two tissues most rarely infected with tuberculosis are muscle and fat. In these cases of peritoneal tuberculosis, there is, of course, a tuberculous peri-gastritis. Between the serosa of the stomach and the musculature there are no lymph follicles, and it is doubtful whether there is any flow of lymph in the direction of serosa to mucosa. Assuming this to be true, the rarity of involvement of the gastric wall in cases of advanced peritoneal tuberculosis can be at least partially explained on the basis that there is an immune tissue, namely, muscle, between the infection and the site of election for the best growth of a tuberculous process,—the lymph follicles.

Hurst and others have concluded that the tuberculous involvement of the stomach in their cases was due to infection of chronic gastric ulcers by tubercle bacilli from swallowed sputum. Collinson and Stewart in 1928 presented the following statistics: In 1000 consecutive autopsies, 86 of the cadavers, or 8.6 per cent, were tuberculous. In autopsies on 151 cases of acute gastric and duodenal ulcer, 5 cadavers, or only 3.4 per cent, were found to have active tuberculosis. In autopsies on 282 cases of chronic ulcer or scarring of the stomach and duodenum, only 8 cases, or 2.1 per cent, had active tuberculosis. The conclu-

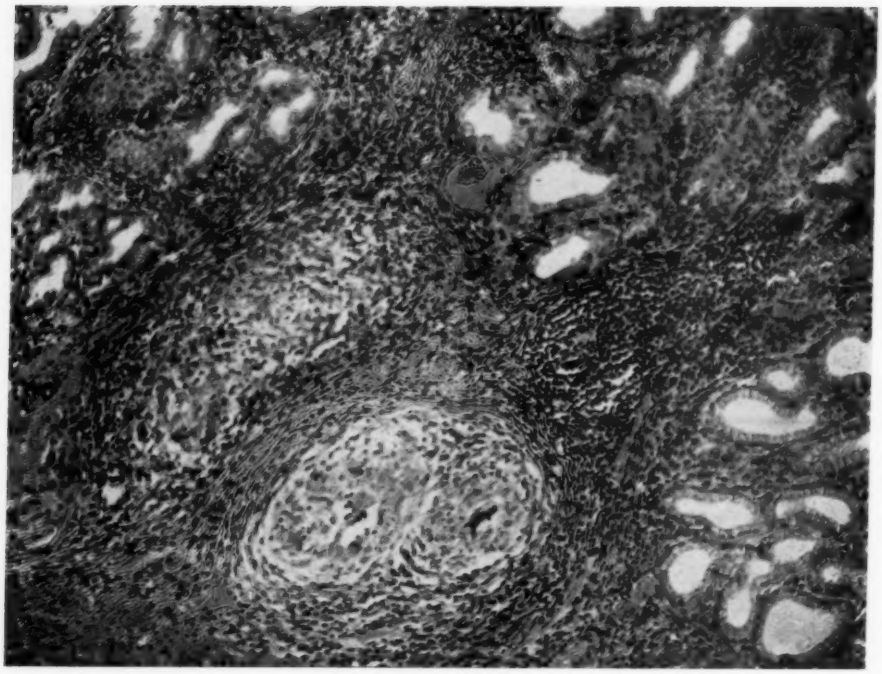

FIG. 3. Miliary tubercles in submucosa near border of gastric ulcer.

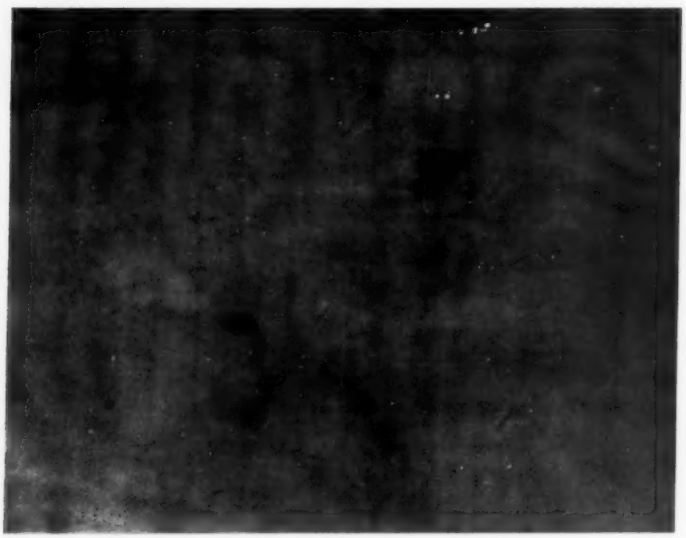

FIG. 4. Oval acid-fast bodies in miliary tubercles of gastric mucosa. Much's granules (?). x 1500.

sion that one might draw from these figures and the addition of deductions such as Hurst made relative to his case is that the rarity of gastric tuberculosis may be partially explained on the basis of constitutional pecularities. The constitution which is likely to develop gastric ulcer is not the type that acquires tuberculosis readily.

It seems logical to us that the factor of speed of passage of infective material through the stomach is important in explaining the rarity of gastric tuberculosis. The view that tuberculous enteritis is usually the result of infection through the mucosa and Peyer's patches has perhaps the majority of those who have considered the question as its advocates. Yet it seems to be that the relative stasis,—the period of time during which a given bit of infective material may remain in contact with a given portion of mucosa, is an important factor. The slowness of passage of infective material plus the richness of the submucosa in lymph follicles, in explaining the frequency of tuberculous infection of the ileum, aid us in concluding that the rarity of tuberculous infection of the stomach may be partly explained by the rapid emptying of its contents (by hyperperistalis in some of the cases of ulcers of the lesser curvature when the patient is swallowing tuberculous sputum), and by the relative rarity of the lymph follicles of the stomach as compared to the rest of the intestinal tract.

### Case Report No. 1

E. S., case No. 199452, male, aged 55, a white American laborer was admitted to the Medical Service of the University of Michigan Hospital August 2, 1928, complaining of cramps in the stomach.

*Present Illness*: Following influenza in 1918, the patient began to have attacks of very severe pain in the pit of the stomach. The pains were sharp, radiated up under the sternum and were severe enough to double him up. They were not related to meals. They lasted five to fifteen minutes and were relieved by vomiting. The vomitus was sour, bitter and yellow. After the pain was gone the patient had a feeling of distension and soreness in the upper abdomen. The attacks of pain at first occurred only every two or three months, but increased in frequency so that recently they had occurred at least once a week and sometimes two or three times a day. The diffuse soreness and distress had been constant for the last few weeks. There was never any jaundice or clay colored stools. There was no history of contact with lead. Venereal disease was denied. The patient had never vomited blood or noted tarry stools. He had suffered a gradual loss of 20 pounds in weight during the past two years. His appetite had been poor for a year. He was not troubled by constipation, but had occasional slight attacks of diarrhoea.

*Past History*: Whooping cough, chicken pox and diphtheria occurred during childhood. He had measles at the age of 20, typhoid at 30, and influenza at 45. There had never been any dyspnea, palpitation, pain in the chest, cough, hemoptysis or night-sweats. There never were any gastrointestinal symptoms aside from those in the present illness. There had been no genitourinary complaints, no disturbance of sleep or memory, no nervousness nor ataxia. The marital history was not remarkable. The only thing of note in the family history was that the patient's mother was thought to have died of tuberculosis at the age of 44.

*Physical Examination*: The patient was a well developed, fairly well nourished male who appeared to be of his stated age, and intelligent. Pupillary reflexes were normal. Several teeth were missing and those present were carious, with marked pyorrhea. There was no lead line. The tongue had a gray furred coat. The thorax was normal

in size and shape. The rate, depth and character of respirations were normal. The heart was not enlarged; the beat was regular and of normal force. There was a loud blowing systolic murmur at the apex. There was no increase in width of retromanubrial dullness. The blood pressure was 148/90. The lungs showed no abnormality of tactile fremitus, resonance, voice or breath sounds. There was no tympany, dullness or flatness. *Abdomen*: There were no visible superficial veins. The level was slightly below that of the chest. The panniculus was thin. No patterns or peristaltic movements were noted. The abdomen was symmetrical. There were no pulsations, masses, spasm, herniae or fluid. Respiratory movements were normal. No viscera were palpable. There was tenderness in the epigastrium on deep pressure. There was no costovertebral angle tenderness. The *genitalia* showed no abnormalities. The *prostate* was apparently normal. The extremities were normal in every respect aside from a moderate arteriosclerosis. *Bones* and *joints* were apparently normal. There were no palpable lymph glands in the neck, axillae, groins or epitrochlear regions. There were no skin lesions.

*Neurologic Examination* was negative.

*Laboratory Findings: Urine*: Yellow in color, specific gravity varied from 1.013 to 1.024. There was never any albumin or sugar. Centrifuged sediment showed no red blood cells or casts. There were two or three white blood cells per high power field. *Stools*: Medium brown, semi-formed, Benzidene and guaiac tests were repeatedly negative. No mucus, parasites or ova were found. *Blood*: Hemoglobin, 104 per cent; leucocytes, 9,450 per cubic millimetre. The Kahn reaction was negative on the blood. *Gastric Analysis*: The fasting specimen was greenish in color, contained no food, blood or mucus. Free acid was 25°, combined acid 11°, total acidity 36°. The specimen taken 45 minutes after the test meal showed some food, no blood or mucus. Free acid was 49°, combined 20°, total acidity 69°. The specimen 90 minutes after the test meal showed some food, no blood or mucus, the free acid was 64°, combined 10°, total acidity 74°.

*X-Ray Findings upon Admission: Lungs.* There was an accentuation of the hilar shadows and bronchovascular markings. Numerous small calcified areas were seen in the outer margins of the hilar shadows. There was a small group of areas of increased density in the left apex. These findings were interpreted as indicative of an old pulmonary tuberculosis, activity to be determined through clinical examination. *Gastro-intestinal X-Rays*: The gall bladder was well visualized. There was a constant defect in the lesser curvature, which had the appearance of an ulcer crater. The duodenal bulb appeared spastic and showed a persistent deformity due either to another ulcer or a reflex spasm from the gastric ulcer. There was 16 per cent retention at six hours. The caecum was movable and not tender. The appendix was visualized, fixed, segmented, and not tender.

*Course in Hospital*: A diagnosis of chronic gastric ulcer was made. Surgical treatment was deemed advisable and on August 17, 1928, operation was performed under nitrous oxide anesthesia. Exploration revealed a moderate amount of perihepatitis. The gall bladder appeared normal and emptied easily. The spleen, large and small bowel were normal. The appendix was not felt. There was a scar on the anterior surface of the duodenum close to the pylorus characteristic of an old duodenal ulcer. On the lesser curvature of the stomach, 7 centimeters above the pylorus, was an ulcer with a crater 5 millimeters in diameter surrounded by 2 centimeters of induration. Partial gastrectomy was done, removing the lower third of the stomach. Closure was affected by the method of Polya, and the abdominal wall closed in layers.

The patient's convalescence was uneventful. He vomited twice on the third day post-operative. His nausea and vomiting and gastric distress were successfully combated with flaxseed poultices, intravenous glucose, and gastric lavage with warm bicarbonate of soda solution. From the fourth day post-operative he felt very well. Sutures were removed on the tenth day. On the

twelfth day, X-Ray showed the gastroenterostomy to be functioning perfectly and the patient was up and about the ward. On August 30th, thirteen days post-operative he was discharged home on a Mills IV diet.

At no time during the stay in the hospital were the pulse, temperature or respirations alarming, nor did they point to any activity of a tuberculous process.

*Pathologic Examination*: The lower third of the stomach was received in formol. Grossly it showed only what appeared to be an ordinary chronic gastric ulcer about 6 millimeters in diameter with considerable fibrosis extending around it and through the gastric wall. Sections cut at various levels through the ulcer showed it to be the usual type with callus extending entirely through the musculature. In addition, there was, as shown by serial sections, almost a solid ring of epithelioid and giant cell tubercles in the solitary lymph follicles surrounding the margin of the ulcer. Blocks from the gastric mucosa at a little distance from the ulcer showed fewer or no tubercles. Several small regional lymph nodes were completely filled with non-caseating miliary tubercles.

Persistent attempts to show the characteristic rods of tuberculosis by modifications of the Ziehl-Neelson staining method were futile. However, within the tubercles, and at no other place, globular and ovoid bodies, varying from one micron to four microns in diameter, and staining a bright red by the acidfast method, were shown. Some of these bodies appeared to lie extra-cellular; a few were definitely within the giant cells.

No spirochetes could be found after many attempts to stain them.

*Case Report No. 2*

L. N., case no. 199452, male, age 5 years, of Mexican descent was admitted to the Pediatrics service August 5, 1926, his parents complaining that he had been sweating a great deal, that he had no appetite, and that he had become very weak.

*Present Illness*: The child began to lose weight five months prior to admission, grew weaker and went steadily down hill. A month before entrance he began to cough. The cough became progressively worse. He did not complain of pain.

*Past History*: Diphtheria at the age of two. No other contagious diseases.

*Family History*: No tuberculosis. Venereal diseases denied.

*Feeding History*: Breast fed until one year of age.

*Physical Examination*: A male child, breathing rapidly with dilatation of the alae nasi, sweating about the face and apparently acutely ill. Eyes wide open with a lateral nystagmus. *Head*: No abnormalities of the skull or scalp. *Eyes*: Pupils equal, react to light. No conjunctivities or keratitis. *Ears* and *Nose*: Negative. *Mouth*: One carious molar. Tonsils are of medium size, not septic. *Neck*: Palpable cervical glands, not definitely enlarged. *Chest*: Mild rachitic rosary present. Normal expansion on both sides. *Lungs*: Marked dullness throughout the area of both lungs. Breath sounds bronchial in type. Numerous coarse râles heard throughout the parenchyma of both lungs. *Abdomen*: Prominent and rigid. No masses could be felt but there was dullness in each flank. *Extremities*: Atrophy of the musculature. Edema of the ankles and feet. *Reflexes*: Knee jerks present, diminished. Babinski and Chvostek's signs not present. *Impression*: Miliary tuberculosis, tuberculous peritonitis.

*X-Ray Findings*: Trachea, heart and mediastinum displaced to the left. Both halves of the diaphragm partially obscured. Right costophrenic angle practically obliterated. The right lung field presented a pneumothorax at the apex to about the 3rd rib anteriorly, with a caseous consolidation from the second to the sixth ribs anteriorly and mottled lung below. Left lung field was encroached upon by heart and mediastinum; that part which was free was mottled throughout.

*Urine Examination*: Essentially negative, except for a few white blood cells in the sediment.

*Blood Examination*: Wassermann test not done. Hemoglobin 70 per cent, red

blood cells 4,440,000, white blood cells 18,000. Differential: Polymorphoneutrophils 56 per cent, small lymphocytes 20 per cent, large lymphocytes 18 per cent, transitionals 6 per cent.

*Spinal Fluid Examination*: Pressure normal fluid clear. No increase in globulin. Sugar 0.081 per cent. Culture negative.

*Tuberculin Test*: 0.1 milligram each of old tuberculin, human and bovine, intradermally showed positive reactions at 24 and 48 hours.

*Course while in Hospital*: The child went steadily down hill; coughing could not be controlled by paregoric. Perspired a great deal, took very little food. Frequently cyanotic, respirations became more and more labored. The temperature varied from 97° F. to 102° F., the pulse averaged 135, respirations from 25 to 40 per minute. The patient expired five days after admission.

*Autopsy* was performed 12 hours post mortem. The gross pathological diagnosis was as follows: Advanced pulmonary tuberculosis with caseous pneumonia. Active chronic caseating peritoneal tuberculosis. Generalized miliary tuberculosis. Tuberculous ulceration of Peyer's patches. Early tuberculous leptomeningitis. Chronic adhesive pleuritis. Chronic adhesive perisplenitis and perihepatitis. Ascites. Left-sided hydrothorax. Fatty infiltration of the liver. Parenchymatous degeneration and acute passive congestion of all organs.

The *microscopic findings* on the autopsy material which are of interest were as follows:

*Brain*: Congestion and oedema of meninges and brain substance. No tubercles found.

*Heart*: Epicardium thickened. Areas of epicardial adhesions. Small foci of mononuclear infiltration beneath serosa, some showing caseating young miliary tubercles. Atrophy of myocardium with marked subendocardial fatty degenerative infiltration. Serous atrophy of subepicardial fat.

*Lungs*: Acute passive congestion. Numerous tubercles in all stages from young miliary tubercles to large caseous masses of conglomerate tubercles. Large parts of lung are completely replaced by caseation with very little tuberculous granulation tissue, the lung architecture being visible only in small areas. In these places the picture was that of a caseous pneumonia. Pleura much thickened by edematous connective tissue containing masses of caseating tubercles.

*Bronchial Nodes*: Completely replaced by masses of confluent caseating tubercles.

*Larynx*: Edematous.

*Thymus*: Fatty atrophy. No tubercles found.

*Spleen*: Many large caseating tubercles, also areas of caseation without tubercle formation.

*Large Intestine*: Caseating tubercles, some of them confluent in the serosa and subserosa. No tubercles found in the mucosa or submucosa.

*Small Intestine*: Large masses of caseating tubercles in subserosa, muscle coats, and submucosa. Tuberculous ulceration of Peyer's patches. By modifications of the Ziehl-Neelson staining method, typical tubercle bacilli were found, shaped as slightly curved rods with beading, on the mucosa, clinging to the surface of the ulcers, and within the tuberculous lesions in the depths of the tissue.

*Stomach*: (The gross examination of the stomach was negative). Chronic catarrhal gastritis. Lymphoid tissue hyperplastic. Groups of multinucleate giant cells in lymphoid tissue, representing early miliary tubercles. There was no ulceration. Modifications of the Ziehl-Neelson staining method failed to demonstrate typical tubercle bacilli within these lesions as rods. However, acid-fast bodies identical with those found in the tubercles in Case No. 1 were found in the tubercles in the submucosal lymphoid tissue of the stomach in this case. Spirochetes could not be found.

*Pancreas*: Post mortem change. Caseating tubercles in suprapancreatic lymphnodes.

*Liver*: Marked fatty degenerative infiltration particularly in the peripheral part of the lobule. Numerous miliary tubercles, many showing caseation.

*Gall Bladder*: Negative.

*Adrenals*: Large masses of caseating tubercles in the peri-adrenal tissue, invading the adrenal cortex by direct extension. Small miliary tubercles in the substance of the adrenal.

*Kidneys*: Passive congestion. Cloudy swelling. Fat dye showed no lipoidosis. Occasional miliary tubercles in the kidney substance.

*Ureter*: Negative.

*Retroperitoneal Lymph Nodes*: Completely replaced by masses of confluent caseating tubercles.

*Testes*: Edematous. Infantile.

*Urinary Bladder*: Negative.

## Discussion

From the clinical and pathological consideration of these two cases, we deduce that the mode of infection of the stomach with tuberculosis in Case No. 1 was similar to the cases described by Hurst and others—infection of a chronic gastric ulcer by tuberculous sputum (or, at least, by tuberculous material within the lumen of the stomach, whether it has entered there by means of swallowed sputum, infected milk, or anti-peristalsis from the intestines). Our reasons for believing this are:

(1) The clinical history of the present illness extended over a period of ten years.

(2) The amount of scarring about the ulcer indicated that it was probably several years old.

(3) From the size, number, proportion of lymphoid, epithelioid, and reticulo-endothelial elements, and absence of caseation in the tubercles, we judge them to be fairly young. Further, from the same considerations, we judge the tubercles within the regional lymph nodes to be younger than those in the lymph follicles immediately surrounding the ulcer.

In case No. 2, with very early miliary tubercles in the submucosal lymphoid follicles, and widespread miliary tuberculosis elsewhere, it seems only reasonable to conclude that the process in the stomach is merely part of a general lymphogenous dissemination.

Heretofore, in order to establish an absolute diagnosis, it has been deemed necessary to demonstrate tubercle bacilli in the depths of the lesions. In our cases, as well as in the cases of many others with excellent histologic and presumptive evidence that the lesions were definitely tuberculous, no typical rod-shaped organisms could be shown by acid-fast stains. We believe, however, that our finding of the acid-fast bodies within the tubercles, although these bodies are of globular or ovoid form, lends support to the histologic evidence of tuberculosis. Whether these acid-fast bodies are degeneration forms of the tubercle bacillus or evidence of pleomorphism we are not certain; they may perhaps be allied to the granules described by Much. Our reasons for attaching importance to them in substantiating the histologic findings are as follows:

(1) They occur only within areas of inflammatory reaction which fit the accepted description of tubercles. They do not occur in other places in the sections.

(2) In certain places in the sections in both cases, these bodies are found

within the giant-cells, apparently having been phagocytized.

(3) They do not resemble connective tissue elements which are known to retain the acid-fast stain.

(4) They are not degenerating erythrocytes within capillaries or lying in the tissue,—elements which retain the acid-fast stain.

(5) Identical acid-fast staining bodies can be shown on the serosal side of lesions in some cases of tuberculous entero-colitis, and what is apparently a transition from the rod-shaped organisms to the globular acid-fast forms can be traced in layers from the mucosal side toward the serosal side.

In the technical work required in the preparation of these cases we experienced some of the feelings which other observers have had, when faced with the problem of establishing the diagnosis by the demonstration of the acid-fast staining rod-shaped organism, they have been unable to do so. We have a strong feeling that many of the cases which in the past have been qualified as only "probable" because nothing more than the histologic description could be given to support the diagnosis would be put on even a firmer basis if the acid-fast bodies which we have seen within the lesions in our cases had been described and recorded.

## REFERENCES


(1) Broders, A. C.: Tuberculosis of the Stomach. Surgery, Gynecology and Obstetrics, 1917, 25: 490-504.

(2) Razzaboni, G.: Gastretomia subtotale per tuberculosi gastrica a forma pseudoneoplastica. Il Policlinico, sez. chir., May 15, 1919, 26: 153.

(3) Geuken, H. C.: A case of Tuberculosis of the Stomach and its Surroundings. Archives of Radiology and Electrotherapy. 1920, 24: 354.

(4) Suermondt, W. F.: Een Geval van Tuberculose de Maag. Nederlandsh Tijschrift voor Geneeskunde, 1925, 69: 2335-2341.

(5) Hurst, A. F.: Chronic Tuberculous Ulcer of the Stomach. Guy's Hospital Report. 1925, 75: 428-431.

(6) Lundgren, A.: Dilatation oesophagienne provenant d'un rétrécissement tuberculeux du cardia. Acta Chir. Scandinav. 1926, 61: 172-180.

(7) Faltin, R.: Gleichzeitiges Vorkommen von Tuberculose und Carcinom im Magen. Acta Chir. Scandinav. 1927, 61: 331-338.

(8) Collinson, H. and Stewart, M. J.: Chronic Peptic Ulcer of the Stomach with Acute Miliary Tuberculosis of the Gastric Mucosa. British Journal of Surgery. 1928, 15: 626-634.

(9) Willerding, H. J.: Tuberculosis of the Stomach. Arch. f. klin. Chir. 1924, 128: 109-177.

(10) Duerck, H.: Cited by Broders, loc. cit.

(11) Zagari: Cited by Broders, loc. cit.

(12) Strauss & Wuertz: Cited by Broders, loc. cit.

(13) Carriere: Cited by Broders, loc. cit.

# Christian's Syndrome and Lipoid Cell Hyperplasias of the Reticulo-Endothelial System

By R. S. Rowland, M.D., *Detroit, Michigan*

CHRISTIAN'S Syndrome of Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus is a rare syndrome of early childhood.

Recently, (Archives of Internal Medicine, November 1928), I discussed fourteen cases of this condition, twelve that had been reported in the literature and two new ones of my own, bringing them into relationship with several similar cases that had been recorded as a special form of xanthoma.

The entire group I regarded as a generalized xanthomatosis, representing pathologic lipoid storage, or lipoid cell hyperplasia, of the reticulo-endothelial system.

The pathologic change in these cases occurred as hyperplastic plaques and nodules arising from the areolar tissue, especially of the dura, periosteum, pleura and peritoneum and also to a less degree, as a more diffuse process, in the interstitial tissue of various organs, particularly, the liver, lungs, lymph nodes, bone marrow, spleen, glands of internal secretion and certain nerve structures.

As the clinical and anatomic features of Christian's Syndrome have not been generally discussed, in this manner, up to the present time, I wish to consider these features in so far as records permit and in so doing, give further reasons for correlating the different lipoid cell hyperplasias of the reticulo-endothelial system, which this unique syndrome suggests.

Considered in all its many forms lipoid cell hyperplasia of the reticulo-endothelial system cannot be regarded as a rare condition and this remarkable pathologic storage of lipoids in the body presents so many problems of general medical interest, it should be better known.

H. A. Christian, in 1919, first drew attention to this unique syndrome under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, an Unusual Syndrome of Dyspituitarism," reporting a case presenting this symptom complex and citing two similar cases previously described by Schüller. Hand, in 1921, discussed three more cases, including one previously reported by Kay. Since then Grosh and Stifel, Thompson, Keegan and Dunn, Danzer, and Kyrklund have each reported one case. Recently I have added two more cases of my own to this list.

Three cases recorded in the dermatological literature, which resemble this syndrome, were reported by Pusey and Johnstone, Spillman and Watrin, and Weidman and Freeman. I wish, especially, to draw attention to the lat-

ter case in which the clinical report was made by Griffith.

There are several cases recorded in the literature under the title "Multiple Myeloma of Childhood" which also resemble this syndrome. I have included one of Berkheiser's as Maximow regarded some of the lesions as xanthomatous in character. A case reported by Schulz, Wermbter and Puhl under the title "A Granuloma-like System Disease of the Hematopoietic Apparatus; Hyperplasia of the Reticulo-Endothelial System" is typical of the syndrome and recently, H. Herzenberg has reported the same clinical picture under the title "Die Skelettform der Niemann-Pickschen Krankheit."

These cases all occurred in early childhood, but there are also somewhat similar adult cases, and since my paper in November 1928, I have learned of a number of unpublished cases, and received one case report from D. S. Milne of New Zealand, which had been previously reported by W. R. Stowe.

It is this group of seventeen cases, fourteen of which were presented less fully in my previous paper, that I wish to discuss, as I believe that they represent a fairly definite group showing massive lipoid storage, or lipoid cell hyperplasia of the reticulo-endothelial system, as it occurs in early childhood.

### Resumé of Cases Showing Christian's Syndrome

Christian's patient, a girl, aged 5 years, was normal until 3 years of age, at which time her teeth became loose and her gums swollen and tender. She had never been ill, except that she had had mumps three or four months previously. When she was 3 ½ years old she developed thirst and polyuria, the right eye became prominent, and she complained of more or less pain in the head. Examination at 5 years showed defects in the bones of the skull, exophthalmos, loose teeth with swollen gums, some of the teeth missing, and typical diabetes insipidus. X-ray study of the entire skeleton showed extensive defects in the skull bones, slight but similar defects in the flat bones of the pelvis and a quite normal appearance and normal stage of ossification and development in the other bones of the body. "The defects in the skull caused an appearance which can be best described by comparing them to the irregular holes in a bit of moth-eaten flannel, or the appearance of a pasteboard box gnawed full of holes by mice." Blood examination showed a red blood cell count of 5,200,000 and a white cell count that ranged between 6,600 and 12,600, with an occasional rise to 14,100, 15,600 and 20,100. The differential count, on admission, showed polymorphonuclear cells 30 per cent, lymphocytes 45 per cent, large mononuclears 23 per cent and eosinophiles 2 per cent. The Wassermann and tuberculin tests were negative. Neurologic symptoms were not present. Christian considered the condition as probably due to disturbed pituitary function.

Schüller's first patient, a boy aged 16 years, had a severe fall on the abdomen at the age of 6 years. Following this accident he suffered nocturia. His growth was retarded and he later developed the picture of dystrophia adiposogenitalis. When he was 12 years old, a discharge began from his

left ear. Exophthalmos was first observed at the age of 15 years. Examination at this time showed extensive cranial defects. On both sides of the neck above the clavicle were "fatty tumors." Schüller ascribed the condition to a tumor at the base of the brain, an angioma of either the dura or skull bone.

Schüller's second patient, a girl of 4 years, was normal up to the age of 1½ years, at which time she had whooping cough. When 2 years old she developed thirst and polyuria, and exophthalmos was first noted. At the same time extensive defects in the skull were demonstrated. X-ray of the pelvis showed a defect in the right ilium, also a spindle-like thickening in the upper part of the right femur. She was under observation for a number of years, during which time there was some retrogression in the defects of the skull. The diagnosis was "anomaly of the skeleton resulting from disease of the hypophysis."

Hand's first patient was a boy, aged 3 years, who complained of thirst and polyuria, which had begun eight weeks previously. He had had enterocolitis at 5 months and measles and croup at 2 years. The child was undersized and poorly nourished, with light brown hair and bronzed dry skin. His abdomen was distended and tympanic obscuring, at first, a very large liver and spleen. The skin of the abdomen was covered with petechiae and "an eruption something like scabies." Later these spots increased in number and were elevated, appearing over the body and extremities. His eyes were in a condition of exophthalmos and the head was bent forward, giving him a "frog-like" appearance. Polyuria and polydipsia were pronounced. At autopsy, when the scalp was removed, a yellow nodule the size of a five cent piece was noticed near the right parietal eminence. When the skull cap was removed, this nodule was seen on the inner side, evidently arising from the dura, and there were other similar areas eroding the skull. The lymphatic glands in the mesentery, mediastinum and all through the body were enlarged. Bronchopneumonia of both lungs, caseous pleuritis of the right lung and warty endocarditis of the mitral valve were found. The liver and spleen were enlarged and firm and had minute gray nodules in their substance. The kidneys were only slightly enlarged, but with the same change. In the pelvis of each kidney was a hard yellow mass. The diagnosis at the time was tuberculosis, but Hand stated that he doubted the diagnosis himself.

Hand's second case, originally reported by Kay under the title "Acquired Hydrocephalus with Atrophic Bone Changes, Exophthalmos and Polyuria," was in a boy, aged 7 years, who had been healthy up to 4 years, at which time he had scarlet fever followed by a persistently discharging right ear. Four months after the scarlet fever, he had swollen cervical glands. When he was 4½ years old, the "gums began to separate from the teeth." This was followed by a gradual loss of his teeth, beginning with the molars. At the same time soft spots appeared on the head where there seemed not to be any bone. When he was about 5 years old, exophthalmos was observed and shortly afterward

polyuria and thirst suddenly developed. He passed 27 quarts of urine daily. He was much undersized for his age. It was observed that his breathing was stertorous. The bones were normal except for very extensive cranial defects and similar changes in the maxillae. Kay evidently thought that the condition was due to a tumor at the base of the brain.

Hand's third case was in a boy, aged 4 years, who had had a tumor-like swelling removed from the left parietal region at the age of 2 years. There had been an absence of bone at this point, the mass seeming to arise from the dura. The pathologic report of the tissue removed was "No gumma, no sarcoma, slight degree of inflammation, mainly a myxomatous change." Since then other swellings had appeared and exophthalmos, greater on the left side, had developed. In this report Hand stated that "no polyuria has developed as yet." The x-ray showed marked cranial defects, but "no involvement of the sella turcica," and "so no symptoms of diabetes insipidus."

Grosh and Stifel's patient, a girl, aged 7 years, was weak and did not develop from the second year. She was markedly underweight and underheight. At 6 years she began having trouble with her teeth and with the left mastoid, which was opened and drained. Her mouth became sore with a bullous eruption on the gums, which necessitated the removal of some of the unerupted permanent teeth. Seven weeks after the operation on the mastoid she suddenly developed polyuria and thirst. Examination at 7 years showed a bad condition of the teeth and gums, extensive cranial defects, dwarfism, typical diabetes insipidus and unilateral exophthalmos. There were similar bony defects of the maxillae and left ilium. When she was observed three years later, there was hardly any increase in her size, no obesity and the genitals were normal. The left ear was still discharging. The cranial defects had increased slightly. There was no x-ray evidence of involvement of the sella turcica.

Thompson, Keegan and Dunn's patient was a pale, poorly nourished boy of 9 years. At the age of 7½ years, he had a severe attack of measles. Following this, he was in a weakened condition and the gums became sore and the teeth loosened. Six months after the measles, excessive thirst and polyuria suddenly developed, persisted for a few days and then disappeared. At this time, soft spots on the right side of the head were observed. A year after he had had the measles, polyuria and thirst again appeared. The boy was emaciated, with a sallow skin. There was moderate exophthalmos, marked gingivitis and clean and sound but loose teeth. The x-ray showed extensive bony defects of the skull, described as "geographical skull." The sella turcica appeared normal, but there were extensive similar defects in the maxillae, pelvic bones, upper portion of the right femur and ribs. The body of the fourth lumbar vertebra was collapsed. A tentative diagnosis of multiple myeloma was made. This patient was under observation about eighteen months, during which time he grew progressively worse. He became pale and emaciated, suffered from backache and pain in the left hip and

walked with a marked limp, listing forward to the left. Exophthalmos was marked. The entire skull was soft and doughy, with only an irregular framework of supporting bony ridges. The gingivitis was severe, and the teeth were held by soft investing tissue as the alveolar processes had been absorbed. An x-ray of the chest revealed a diffuse increase in density, characteristic of chronic interstitial pulmonitis. As death approached, the cough and dyspnea became more troublesome. The end came suddenly, and was attributed to impaired circulation incident to intense pulmonary fibrosis. At autopsy, the scalp showed fibrous adhesions. The inner surface of the dura was mottled by dull yellowish white tissue, which took Sharlach R fat stain. The large yellow infundibulum stalk was fibrosed. There was involvement of the middle ear and of the petrous portion of the mastoid. The ethmoid cells were obliterated by the same tissue growth. The pathologic diagnosis in the case was "exophthalmos; decalcification of bones; fibrosis of the tuber cinerum; slight subacute inflammation of the pars posterior of the pituitary gland; chronic interstitial fibrosis of the lungs; hypertrophy of the heart; chronic passive congestion of the liver and spleen; hypertrophy of the kidneys and bladder." From their histologic study, Thompson, Keegan and Dunn considered the condition "inflammatory, rather than degenerative or a primary metabolic (endocrinologic) process."

Danzer's patient was a boy, aged 4 ½ years, who had recently had his tonsils removed. He was miserable, having had repeated attacks of sore throat. Two months after the operation, his mother first noticed soft tender spots on his head. He was pale and stoop-shouldered, with exophthalmos, bad teeth, spongy gums and many soft spots on his head. He complained of thirst and polyuria, which had evidently developed suddenly a year after the soft spots were first observed. The x-ray showed extensive cranial defects and similar changes in the maxillae. Danzer makes no comment regarding the bones of the rest of the body and does not discuss the etiology.

Kyrklund, under the title "Thinness of the Skull, Exophthalmos, Dystrophia Adiposogenitalis and Diabetes Insipidus," reports a case. His patient, a girl, aged 12 years, was normal up to the age of 2 years, at which time she developed a cough, began breathing rapidly and became emaciated. At 4 years she developed thirst and polyuria. At the age of 7, she suddenly became fat, walked stiffly and complained of pain in the legs. The skin of the head was so tender that she could not stand having her hair combed. Growth was noticeably retarded, as was mental development. She was dyspneic. Her lips, hands and feet were cyanotic. She had the typical appearance of dystrophia adiposogenitalis. Examination showed that there were numerous cranial defects. The long bones were normal. The teeth were in a bad condition and exophthalmos was present. At autopsy, the scalp was adherent to the calvarium around the soft areas and when separated, yellow detritus-like material flowed out leaving cyst-like depres-

sions. The inner table in these places was eroded and the space filled with brownish yellow tissue arising from the dura. The dura had grown firmly to the inner table and showed yellowish brown, tumor-like thickenings. The region of the hypophysis did not show macroscopic changes, but there were growths in the brain stem behind the hypophysis of the same brownish yellow color. There were extensive changes in both lungs and pleura. "The structure of the lesions, on the whole, was similarly formed of connective tissue cells, part round cells, and some spindle cells. Lesions in the brain stem contained irregularly formed giant cells. The histological process did not simulate tuberculosis." Kyrklund considered the "condition due to a tumor of sarcomatous nature," and believed the "diabetes insipidus secondary to the growth in the region of the hypophysis."

Milne's patient was a quarter-cast Maori boy, aged 3 years, who had been suffering from three months from loss of appetite, polydipsia and polyuria, together with exophthalmos, particularly on the right side. He had an ertensive discrete papular eruption on the chest and back, many of the papules being surmounted by small oval crusts of seborrheic appearance, which, in certain parts, appeared infected and erythematous. The child was peevish and puny, although of normal mentality. The skull on x-ray examination presented many deficiencies in the cranium. In plates taken 9 months afterwards, the skull defects appeared smaller. His last weeks were marked by an irregular temperature and troublesome bronchitis. Autopsy: On reflecting the scalp, a number of swellings resembling putty in appearance, but of fairly firm consistency, were observed. These areas were extensions, through small perforations in the skull, from the dura which was extensively infiltrated. The brain was normal. A compact yellow mass about the size of a walnut rose up out of the sella turcica, displacing the hypophysis, but without eroding or distorting the clinoid processes. Another mass projected back from the right wing of the sphenoid. It also extended to the ethmoid and both orbits. The histological description of this tissue was: "Striking yellow mass —composed of spindle cells with large clear spaces filled with granular yellow substance. Scattered throughout the tumor were giant cells with rosette nucleus surrounded by a granular zone. The nodules from the dura showed the same changes. The entire pituitary was invaded by the yellow growth." Milne regarded the condition due to a tumor arising in the hypophysis. No report was made of the rest of the body.

(Author's cases recorded in full in the Arch. of Int. Med., Nov. 1928).

My first patient was a boy 5 years old, who was normal and healthy until 2 years of age when, following an attack of measles, he did not seem as well as usual. Six months later a swelling and tender area appeared on his head, ascribed to a fall. When 3½ years old, another swelling appeared. Examination at that time showed a poorly nourished boy with numerous cranial defects, loose teeth, swollen and tender gums and marked exophthalmos. There were no urinary symp-

toms. I first saw him eighteen months later, because of shortness of breath and a difficulty in walking which had increased rapidly during the past three months. He had the bend-over, dwarfish, frog-like appearance described by Hand. There was a slight purulent discharge from both ears. The alveolar arches were swollen and tender, and only three very loose teeth remained in a swollen tender jaw. His skin was not especially dry and he did not show any eruption. There was a slight yellow tint to the skin. He was somewhat cyanotic. Roentgen ray examination showed multiple cranial defects involving the vortex and base of the skull, with very extensive erosion of both upper and lower jaw bones, and a slight defect in the right ilium. The urine was negative. Blood showed: hemoglobin, 57 per cent; red blood cells, 4,150,000; white blood cells, 17,350. Differential: polymorphonuclears, 64 per cent; large mononuclears, 32 per cent; small lymphocytes, 4 per cent. Intradermal tuberculin test was negative. Wassermann reaction negative. The patient grew progressively weaker. His death was attributed to cardiac failure due to impaired circulation resulting from extensive pulmonary fibrosis. Autopsy revealed extreme pallor of the skin and marked exophthalmos. When the calvarium was exposed there were numerous annular defects of the cranial bones. These defects were filled in with a gummy semicaseous, bright yellow tissue of rubbery consistency. On removal of the skull cap, it was found that the tissue could be easily pushed out of the defects, leaving ragged holes in the skull. This tissue appeared to arise from, and be continuous with, the dura. The brain was edematous, but otherwise normal. The base of the skull was covered with plaques of the same yellow granulomatous-like tissue which extended forward into both orbits and completely surrounded the region of the hypophysis. In this region there was extensive bone destruction. There was a marked atrophic process of both middle ears, without destruction of bone. The heart was markedly enlarged. The lungs were voluminous and felt fibrous to palpation. They were adherent in the posterior lateral aspect, with adhesions of the same gummy yellow tissue noted in the granulomas of the dura. On section, the whole lung was a mass of communicating vesicular cavities, varying from the size of a pinhead to that of a pea. The septum between the cavities was fibrous and inelastic. When the ilia were exposed there was found in the eroded area of the right ilium a yellow plaque about 1 cm. in diameter, with a bone defect of the same character as seen in the skull. A similar yellow plaque 2 cm. in diameter protruded from the periosteum on the right side of the body of the first lumbar vertebra. The dural plaques consisted of masses of lipoid-containing cells of reticulo-endothelial type resembling xanthoma. Throughout were numerous multinuclear giant cells. In the old tissue of the dura were numerous small calcareous concretions. In lipoid masses were areas of cholesterol crystal formation, with cholesterol clefts and with many multinuclear giant cells. Giant cells, evidently foreign body giant cells, surrounded the cholesterol crys-

tals. These plaques did not suggest infectious granuloma but resembled xanthoma or masses of cells of the xanthoma type, and probably consisted of proliferated reticulo-endothelial cells with cholesterolosis. Fat stain showed cells to be loaded with lipoids. Chronic bronchopneumonia, with localized patches of fibrosis and alternating patches of emphysema, was found in the lungs. The reticulo-endothelial cells around the pulmonary vessels showed the same hyperplasia and lipoidosis seen elsewhere, and projecting into the larger bronchi were papillary overgrowths of fibroblastic tissue and reticulo-endothelial tissue showing lipoidosis. The pleura was thickened with reticulo-endothelial hyperplasia and lipoidosis. The liver presented marked passive congestion. The lipoidosis was slight in the liver cells, more marked in the periphery of the lobules, and there was some atrophy of the cells. Many lipoid Kupffer cells were found. The lymph nodes showed lymphoid exhaustion of the germ centers. Proliferation of the reticulo-endothelium with lipoidosis and slight pigmentation was present. The proliferation of the reticulo-endothelium and lipoidosis varied greatly in the different nodes, being quite marked in some, while others showed them to a slight degree. All through the retroperitoneal tissue there were bands of the atypical tissue. The bones showed atypical marrow. There was reticulo-endothelial hyperplasia with many multinuclear giant cells and many lipoid cells. Rarefaction of the bony trabeculae was found. (The bone absorption resembled that seen in some cases of osteomalacia.) The muscle fibers of the heart were fairly well developed for this age. Little lipoidosis of the muscle and no reticulo-endothelial proliferation and no lipoidosis in the stroma were found. The testes were apparently normal for the age. Lipoid cells were not found in the testes or epididymis. The kidneys were congested with edema and some lipoidosis of the renal epithelium. Small concretions of lime salt were found in some of the tubules. Proliferation of the reticulo-endothelium and lipoidosis were not found. Sections from the brain did not show any pathologic change except slight edema. The thyroid gland showed a colloid content normal for this age, with undeveloped adenomatous tissue. Throughout the gland, there were a number of sharply circumscribed areas of proliferation of the stroma having an epithelial appearance in the center, with some lipoidosis. The suprarenals showed hypoplasia which was especially marked in the medulla. Moderate lipoidosis of the cortical cells was present. In the perisuprarenal tissue there were small areas of proliferating reticulo-endothelium. The large epithelioid cells showed more lipoidosis and some pigmentation, thus resembling xanthoma cells. In one section in the medulla were small areas of proliferating reticulo-endothelial cells with lymphocytic infiltration. The pineal gland was edematous and congested. Lime salt deposits or lipoid cells were not present.

The clinical diagnosis was membranous bone defects, exophthalmos and dwarfism—Christian's syndrome. Generalized xanthomatosis of a visceral type was found. The condition was

regarded as a particular juvenile form of lipoid cells hyperplasia of the reticulo-endothelial system.

My second patient was a boy, 3 years and 11 months old, who developed normally during the first year. When he was slightly under 2 years, he became irritable, complained of a sore mouth, began to ask for water frequently and pass large amounts of urine. The soreness of the mouth grew worse and several of the back molar teeth loosened and came out. The symptoms of thirst and polyuria were variable. He was treated in the Children's Hospital several months. During this time bone defects were discovered in the skull. There was also involvement of the fifth rib and an area of decreased density in the right ilium. There was some unexplained irregularity in the temperature and his weight fluctuated considerably. When I first saw him 14 months later, his appetite and digestion were good. He complained of only moderate thirst and passed from 6 to 8 quarts of urine in 24 hours. His mother first noticed, at this time, that he had not grown. Examination showed bone defects of the cranium, slight exophthalmos of the left eye, swollen and tender gums. All the molar teeth in both upper and lower jaw were loose. The teeth, themselves, were in a good condition. Roentgen ray examination revealed marked extension of the bone erosion in the skull bones and maxillae and changes in the 5th rib. This patient has been under observation for nearly 3 years. He appears well, has a good color, his polydipsia and polyuria cause little disturbance; more surprising, the bone defects cannot be felt on palpation and he made a fair growth during the time he was under treatment. The roentgen ray examination shows almost complete closing in of the bone defects.

The clinical diagnosis was Christian's syndrome of membranous bone defects, exophthalmos and diabetes insipidus. The condition was regarded as generalized xanthomatosis, a juvenile form of lipoid cell hyperplasia of the reticulo-endothelial system.

Griffith's patient, a much undersized boy of 9 years, had been healthy and normal up to 2 years. At the age of 2½ years, he had pertussis. At 3 years he had a temporary enlargement of the abdomen and "yellowness." Growth was evidently retarded from this time. At 8 years he had another attack of jaundice and swellings on the head following contusion, and an eruption appeared all over the body. The child was undernourished and underdeveloped, with extensive cutaneous xanthoma eruption, evident exophthalmos, marked irregularities of the teeth, defects in the skull and typical diabetes insipidus. The liver was felt 3 cm. below the costal margin, the spleen felt 4 cm. below the costal margin. The post mortem study of this case was made by Weidman and Freeman. The liver was enlarged, slaty green and had the appearance of hypertrophic biliary cirrhosis. There was extensive lipoidosis and fibrosis. The lungs showed the same changes with more fibrosis and localized areas of round cells and some lipoidosis. The cut section of the lungs showed marked fibrosis together with emphysema, yellow mottling could be made out on the cut surfaces. The peribronchial lymph

nodes showed varying amounts of lipoidosis, fibrosis and round cell infiltration. The pituitary was large, firm and bright yellow. In the brain tissue, in this region, there was yellowish lipoid infiltration. This appeared to extend from the meninges inward. The posterior lobe of the pituitary was completely fibrosed, with some lipoidosis; the anterior lobe was found normal. The pineal gland was involved. In the brain, it was thought that the lipoidosis concerned the glia cells. The authors state that many of the organs reflected the general sclerosing effect of a person dying of senility. There were fibrous nodules, also, on the margin of the mitral and tricuspid valves. The spleen was very large and slightly fibrosed. The kidneys showed passive congestion. Suprarenals were small, thin, flat, and reduced in lipoid content. The pancreas was hypertrophic. Weidman and Freeman regarded the condition as a general systemic chronic inflammatory process, resulting either from a metabolic dyscrasia, producing abnormal metabolites or a low grade infection similar to tuberculosis and syphilis.

Berkheiser reported a case under the title "Multiple Myeloma of Children," which appears to belong in the group I am describing. Berkheiser's patient was a girl, aged 3½ years. She had had a normal first year, except for a mild attack of measles at 9 months. Then she developed a severe eczema about the head, which spread to the body. Exophthalmos was first observed when she was 16 months old. Later she complained of pain in the right leg, hip and arm, and had difficulty in walking. She was irritable, had a slight elevation of temperature and gave a history of bed wetting. Examination showed an undernourished, undersized child, with marked exophthalmos and eczema of the scalp. The cervical, axillary and inguinal glands were pea to marble size. The liver and spleen were palpable. There was tenderness over the right inguinal region and posterior to the upper end of the femur. The x-ray revealed extensive bony defects of the cranium, the pelvis, the upper portion of the right femur and the lower portion of the left humerus. Blood: hemoglobin, 44 per cent; red blood cells, 3,500,000; white blood cells, 7,000. Wassermann reaction negative. Urine negative. Biopsy was taken from the skull and right humerus. Tissue was reddish in its peripheral portion, but yellowish in its inner portion, where it had broken down and formed a cyst. Microscopic examination of the soft tissue showed many spherical reticular cells and spindle shaped fibroblasts, many giant cells of foreign body type. In the part away from the periphery were numerous large vacuolated cells, many of them mononuclear but also many of them polynuclear, typical xanthoma cells. The mass was also filled with blood cells, myeloblasts, myelocytes and eosinophiles, blood vessels were numerous. Sections from the skull showed similar changes. Berkheiser's diagnosis in this case was xanthomyelomata.

Schultz, Wermbter and Puhl's patient was an undersized, poorly nourished girl, 2½ years of age. She had a normal birth and was breast fed. She had swollen glands and eczema at 9 months, regarded as scrofula. Her

weight varied greatly, at no time was it normal. When 2 years of age, following measles, she complained of pain in the left temporal region and neck. A yellow swelling appeared on the forehead which was opened and drained. It healed slowly with the formation of a yellow crust. Examination at 2½ years showed an emaciated child, small for her age, with a pale, straw yellow colored skin. There were extensive bone defects of the skull involving, especially, the temporal region, a surprising exophthalmos and enlargement of the cervical glands. Her spleen, the size of a hand, protruded to the level of the umbilicus and the liver was also markedly enlarged. The urine was negative, but the blood showed an extreme degree of anemia —a picture of anemia pseudoleukemia infantum. Blood: 5-20-23. Hemoglobin, (Sahli) 26 per cent; red blood cells, 1,210,000; white blood cells, 6,900. Differential: polymorphonuclears, 67 per cent; large mononuclears, 4%; small lymphocytes, 26%; myelocytes, 1%; basophiles, 1%. 6-6-23. Hemoglobin (Sahli), 17 per cent; red blood cells, 1,250,000; white blood cells, 9,100. Differential: polymorphonuclears, 58 per cent; large mononuclears, 5 per cent; small lymphocytes, 28 per cent; eosinophiles, .5 per cent. Poikilocytosis, anisocytosis, polychromatophilia, 8 normoblasts and megaloblasts in a count of 200 leukocytes. 6-14-23. Hemoglobin (Sahli), 14 per cent; red blood cells, 980,000; white blood cells, 17,800. Differential; polymorphonuclears, 50 per cent; large mononuclears, 7 per cent; small lymphocytes, 36 per cent; young forms, 6 per cent. High grade poikilocytosis, anisocytosis, polychromatophilia, 21 normoblasts in a count of 100 leukocytes. Autopsy showed the following: bone defects of the skull in the frontal and occipital region and very extensive at the base of the skull. A large part of the orbits were transformed into hard fibrous pigmented tissue. The pia mater was thickened. Brain normal. Lungs unusually firm showing grayish yellow nodules. Bronchial and tracheal lymph nodes enlarged. Spleen very large with thickened fibrous capsule. On section, there were many corn size, whitish nodules and some infarct-like lesions near the surface. Pancreas usual size and firm. Liver very large, pale brown, with many scattered grayish nodules like those in the spleen. Peyer's patches swollen. In many parts of the skeleton irregular yellowish white areas were found in the spongiosa. Schultz, Wermbter and Puhl considered the condition a disease of the reticulo-endothelial system and supposed an infection of unknown type to be responsible.

Herzenberg's patient was a girl, aged 5 years, who had always been normal and had had no illnesses, with the exception of measles and pertussis, up to 3 years and 10 months, when she developed a diabetes insipidus, which receded in the course of a year. Later she began to have fever, pains in the head, arms, ribs and legs, and developed a high degree of anemia. Blood: 1-16-26. Hemoglobin, 70 per cent; red blood cells, 4,760,000; white blood cells, 8,800; lymphocytes, 62.5 per cent. 1-11-27. Hemoglobin, 29 per cent; red blood cells, 3,585,500; white blood cells, 11,900; lymphocytes 50

per cent. 12-19-27. Hemoglobin, 9 per cent; red blood cells, 1,030,000; white blood cells, 10,000; lymphocytes, 45 per cent. Platelet count, 22,660. 5 normoblasts in a count of 200 leucocytes, poikilocytosis, anisocytosis, and polychromatophilia. 1-7-28. Hemoglobin, 7.8 per cent; red blood cells, 740,000; white blood cells, 11,000; lymphocytes, 71 per cent. Many normoblasts and megaloblasts. A papulous skin eruption appeared on various parts of the body. The superficial lymph nodes were enlarged, and during observation, the liver and spleen became palpable. She was very irritable, the itchy papulo-pustular eruption increased, there was edema of the face, hands and feet, the temperature fluctuated. Autopsy revealed a well built, but emaciated child, with a pale, slightly yellow skin and an extensive roseola, papular exanthem of the face and trunk. On the forehead were greenish yellow purulent crusts. The cervical, axillary and inguinal lymph nodes were enlarged and on section yellowish red. The surface of the cranium was covered with small light yellow spots giving a mottled appearance. There were numerous bone erosions, in some places, limited to the lamina externa, and in other extending through the diploè and lamina interna, or, limited to the lamina interna. These defects were filled with yellow to dark yellow masses of a soft rubbery consistency. There were larger areas of bone destruction at the base of the skull. In both fossae were yellowish red masses. Similar masses spread over healthy bone, surrounded the thickened infundibulum and extended into the sphenoidal and ethmoidal sinuses. There was no extension into the orbits and no bone erosion about the orbits. The middle ears were filled with a yellow viscid material. On both the inner and outer surfaces of the dura were deep yellow circumscribed map-like deposits, which, in some places, thickened to tumor-like proportions. Here and there, especially on the inner surface, these masses appeared to have a fine hemorrhagic covering. In place of the thymus, there was a dark yellow tumor mass containing fat-like tissue. The heart muscle was fatty spotted. In the aorta there were yellow plaques. In the tonsils there were hazel-nut sized yellow masses. The gastric mucosa was yellowish with lighter spots. Liver slightly enlarged. Under the serosa and on section, near the surface, many dark yellow red bordered nodules were visible. The suprarenals were of normal size, the cortex thin and dark yellow. The spleen was somewhat enlarged and on section there were many grayish yellow, irregularly formed lentil sized areas. In the inner part of the pulp there was a group of yellowish gray areas the size of a cherry cluster. Some of the intraabdominal and periportal lymph nodes were enlarged to hazel-nut size. Those in the mesentery were yellow to yellowish red on section. The bone marrow of the ribs and sternum was dark red, that of the vertebra was dark red with a yellowish ground. There were grayish yellow spots in the marrow, especially in the long bones. Anatomical diagnosis: Niemann-Pick's disease. Splenohepatomegaly. Lipoid cell hyperplasia of the intraabdominal organs, extra and intrathoracic lymph nodes.

Lipoid cell infiltration of the dura mater and skull bones. Hemorrhagic diathesis. Anemia. Histological findings: Lipoid cell infiltration of the skull bones and dura mater. Lipoid cell hyperplasia of all the various infected organs, principally of the skeleton and other organs, which macroscopically appeared unchanged. Pronounced fibrous change in lipoid-containing tissues in the spleen, and especially the femur and skull bones. (Herzenberg considered her case as representing a skeletal form of Niemann-Pick disease).

### General Consideration

*Clinical and Symptomological.* The seventeen cases I have cited as representing Christian's syndrome were in young children. Eight of the patients were girls and nine were boys.

The family histories, in my original group, as far as they were known, did not show any unusual features, with the exception of my own second case, in which a brother had hypercholesterinemia and chronic valvular disease without a rheumatic history, and the mother had hypercholesterinemia and a sallow complexion. But Herzenberg in her recent paper, gives an account of a sister of her patient who had a bronzing of the skin, xanthoma eruption, palpable liver and spleen, and bone defects.

The obstetrical histories were normal and the births uneventful with one exception.

In eleven instances the first manifestations of the disease were during the second year of life, with two in the third year, one in the fourth year, two in the sixth year and one in the seventh. Without exception, there was good health and normal development up to the time of the onset which usually occurred, following one of the common contagious diseases—measles, mumps, whooping cough or scarlet fever. In the course of a few months there was increased irritability, and then either polydipsia and polyuria developed, the gums became swollen and teeth loose, the eyes became prominent or there was a discharging ear which did not respond to treatment.

The progress of the disease was slow at first with remissions, and in milder cases there was very little discomfort, except from thirst and sore gums. As the disease progressed, however, there was increasing irritability, sometimes a low grade unexplained temperature, as well as pain and tenderness in the head, and less often, in the neck, chest, arms and legs. Examination showed the pain to be related to striking bone defects which occurred, particularly, in the flat bones of the skull. The roentgen ray revealed similar, though less extensive, defects in the maxillae, and the flat bones of the pelvis, rarely the scapulae, vertebrae and ribs. Sometimes, the long bones—femur and humerus—had the same bone deficiencies. These areas of bone rarefaction appeared to increase rapidly during the active stage of the disease, but when the condition was inactive, there was an arrest, or, in cases that improved, there was, in the roentgen ray picture, the appearance of a receding of the bone defects.

In the same way the diabetes insipidus sometimes developed suddenly, then gradually subsided or stopped, to appear again later, and the exophthal-

mos varied in degree. In none of the cases was there any evidence of increased intracranial pressure.

For a long time the nutrition was good. Frequently, there was a lemon yellow tint to the skin, sometimes mistaken for jaundice, and a typical xanthoma eruption of the rapidly developing type appeared. The lesions were usually small, scattered irregularly over the face and trunk, papular, with red borders and a yellow center, giving a pustular appearance like the lesions in xanthoma diabeticorum or the rapidly developing congenital type of xanthoma.

Griffith's patient had larger skin lesions, more symmetrically arranged, typical of xanthoma multiplex. It is also of interest that Schüller and Kyrklund described fatty tumors, and Griffith's patient had larger lesions in association with the skin lesions which were probably xanthomyelomata of the tendon sheaths.

In the severer cases, as the disease progressed, it was observed that these children did not grow in a normal manner. They became stunted and emaciated. As a result of the bone defects, deformities arose, and walking became difficult. The spleen, liver and superficial lymph glands were enlarged. Anemia developed to an extreme degree, or there was increasing dyspnea and cyanosis. Death resulted in this severer form in from 2 to 4 years.

The milder cases progressed more slowly. A marked dwarfism became apparent and in two instances, (Schüller's and Kyrklund's patients), in which the affection had extended beyond the seventh year, a typical dystrophia adiposogenitalis developed. In one case, (Pusey and Johnstone's), obstructive growth appeared in the larynx and finally, following intubation and later tracheotomy, death resulted from intercurrent infection, at the age of 18 years.

*Laboratory findings and special examinations.* The urine was normal, except for the variations that usually occur in diabetes insipidus.

The blood changes were fairly definite. In the early stage of the disease there was only a slight degree of anemia with a moderate increase in leukocytes, this increase sometimes being due to a large mononuclear excess. In the advanced stage of the disease a severe rapidly progressive anemia often developed. The hemoglobin and erythrocytes sank rapidly to the lowest level. There was a moderate white cell increase in lymphocytes, poikilocytosis, anisocytosis, polychromatophilia and many normoblasts and megaloblasts. The blood chemistry tests were all normal, except for an increase in blood cholesterol, lecithin and total fats, in several of the cases examined. Blood and spinal fluid Wassermann and tuberculin tests were always negative.

*Anatomical and histological.* The autopsy examinations revealed bone defects preponderating in the skull, but occurring in all parts of the skeleton, and yellow to dark yellow, sometimes brown, rubbery tissue masses arising from the dura, periosteum, pleura and peritoneum. These masses were usually only slightly raised, but sometimes they assumed tumor-like proportions. In the cranial cavity where this proc-

ess was most marked, the tissue growth often surrounded, and appeared to raise the hypophysis up out of the sella turcica; it also extended forward into the orbits, nasal sinuses and middle ear and filled in the bone deficiencies. In Herzenberg's case these masses appeared to arise from both the inner and outer surfaces of the dura and calvarium, but in most instances they were found only on the outside of the dura, and also arising from the periosteum, pleura and peritoneum. In the older and more advanced lesions these rubbery, yellow masses were changed to firm, fibrous, pigmented tissue resembling scar tissue. In places there were cyst-like formations associated with this growth. Many of the organs had the same yellow color. The bone marrow of the long bones, as well as of the flat bones, usually showed changes. Sometimes there was only a darker yellowish tinting, or, there was a grayish to yellow spotting, pin point to barley grain in size. The bone trabeculae were eroded, and in places the erosion extended through the bone, causing large irregular bone defects. In some instances, the hypophysis and neighboring regions of the brain showed the same yellow change. In one case, the hypophysis was entirely sclerosed. The change also occurred extensively in the pleural and abdominal cavities. In both locations there were swollen, yellow tinted lymph nodes, and about the hilus of the spleen, liver and kidneys large yellow masses, of the same appearance, occurred. Frequently, the lungs were unusually firm and showed yellow spotting and extensive fibrosis. When the spleen and liver were enlarged they showed the same change in color and irregular grayish white to yellow accumulations, sometimes cherry size, appeared. Occasionally, the thymus was entirely replaced by such fatty masses. Yellow masses also occurred in the tonsils, esophagus, stomach walls and Peyer's patches. The pancreas was either increased in size or unusually small and fibrosed. The suprarenals were frequently smaller than normal with a decrease in lipoid content. Yellow plaques appeared in the large vessels and on the heart valves. The heart muscle was sometimes yellow spotted. The older lesions in the organs showed the same fibrous change, as in the advanced lesions, at the base of the brain. This was particularly so in the lungs. The lesions in the skin also showed the same yellow appearance, and sometimes fibrotic changes, as seen in the inner organs.

The histological examination showed many lipoid-containing cells in the early rapidly developing lesions, and lipoid cell hyperplasia of all the infected organs. Lipoid cell infiltration of the skull bones and dura, and lipoid cell hyperplasia were also found in organs which macroscopically appeared normal. There was a pronounced fibrous change in the lipoid-containing tissues in the older plaques and tumor-like masses, as well as in the organs—lungs, liver, spleen, lymph nodes, bone marrow, all the glands of internal secretion, the skin lesions and parts of the central nervous system.

Microchemical and chemical analysis showed these cells to contain various lipoids—phosphatid lipoid, chales-

terol and its ester and neutral fats, in varying proportions and amounts.

All the organs participated in this change, if only to a slight degree, the preponderance of change being in the skeletal system, but the severity of the involvement of the different organs varied in each individual case and was not as Herzenberg indicates special to the spleen and liver, for in several instances, the lungs showed the most advanced change and the spleen and liver were only slightly affected.

These changes occurred in the reticulo-endothelial cells of the various tissues and organs involved, and in the advanced stages even extended over into the parenchyma of certain organs, especially of the lung, liver, spleen, kidneys and nervous system.

## Summary

This syndrome presents such a definite clinical and anatomical picture that it seems justifiable to regard these cases as all representing the same condition.

The outstanding clinical features are: the very extensive large irregular, sharply outlined defects in the bones of the skull with similar, though smaller and less numerous, defects in other bones; the frequent occurrence of diabetes insipidus, exophthalmos and persistently discharging ears; the color of the skin; a characteristic skin eruption; sometimes, enlargement of the spleen, liver and lymph glands; a severe progressive anemia or bronchial symptoms with cyanosis and dyspnea; a retarded growth and the occurrence of dystrophia adiposis genitalis.

The anatomical findings which explain the symptoms are: yellow to yellowish brown growths arising from the dura, periosteum, pleura and peritoneum, at times assuming tumor-like proportions; a more diffuse process of the same appearance involving many organs—lungs, spleen, liver, lymph nodes, glands of internal secretion, and parts of the central nervous system and skin; lesions composed of darkly staining nuclei, of reticulo-endothelial origin; frequently, true foreign body giant cells with non-foamy protoplasm; the presence of various lipoids in the foamy cells; fibrous change in the older lesions with almost complete absence of foamy cells; round cell and eosinophile infiltration and other differences depending on the location of the lesions; rarely necrosis and cyst formation.

## Etiology and Pathogenesis

We are dealing with a slowly progressive, general disease, showing familial tendencies, which has periods of remission, but eventually overwhelms the vital organs and brings on death, although sometimes, its course is shortened by an intercurrent affection.

Various theories have been advanced as to the etiology of this syndrome. Pituitary dysfunction was first suggested because of the retardation in growth and the frequent occurrence of diabetes insipidus. One of the most interesting features in this group of cases is the constant and extensive involvement of all the ductless glands.

Naturally, the striking symptom of bone defects has attracted attention, suggesting a variety of conditions causing bone erosion. In a certain stage, this condition might be mistaken for syphilis with its enlargement of

the spleen, liver and lymph glands, but the bone defects are much more extensive and do not resemble the breaking down of a gumma with its resulting scar formation. Also, the many blood tests have been negative for lues and the lesions have not shown suggestive pathology.

Bone destruction in this syndrome appears to arise from hyperplastic areas within the bone marrow, first invading the bone trabeculae and then extending through to the outside. In the skull this may involve either the inner or outer table or include both tables, producing the large defects. The roentgen ray picture also gives this impression. The plaques arising from the dura and periosteum may or may not take part in this change, but in their growth extend to fill in the space formed by the erosion. As the hyperplastic masses in the bone marrow frequently contain many true foreign body giant cells, in my previous paper I suggested that they might be the cause of the bone erosion.

Tuberculosis might be suspected from the occurrence of bone changes and the anatomical appearance of the lesions, but tuberculin skin tests have always been negative and in only one instance was there any family history of tuberculosis. The lesions may show certain resemblances to those of tuberculosis, but they never contain Langerhan's cells, being accumulations of hyperplastic cells filled with lipoids and foreign body giant cells. I might say, parenthetically, that my conception of this disease is such that either tuberculosis, syphilis or a metastatic tumor might be complicated by this change.

In the majority of instances, the cases in this syndrome were regarded as some form of malignant tumor eroding bone—either sarcoma or multiple myeloma. In such conditions, the bone erosions are, frequently, quite as extensive, but the individual lesions are smaller and not so irregular in shape, and the pathology is entirely different.

In the rare cases of leukemia which sometimes are complicated by bone changes, this change is not nearly as extensive and the blood gives a different picture.

Occasionally, because of the massive lesions, an infectious etiology of some unknown form has been thought to be the probable cause of the disease. Schultz, Wermbter and Puhl, in their carefully studied case, considered the process a granuloma of a specific inflammation, partly, because of the fibrosis, areas of necrosis, and the presence of eosinophile leukocytes in the lesions. They believed that they were dealing with a hyperplasia of the reticulo-endothelial apparatus and that a chronic infection was responsible for the marked hyperplasia. But the extent and distribution of the lesions would seem to indicate that this is not an inflammatory hyperplasia. Furthermore, the extensive fibrosis, the rare areas of necrosis, the cyst formation, the round cell and eosinophile infiltration were only found in the older lesions and occurred in the course of their evolution, as secondary changes.

Usually, the massive portion of this infiltration arising from the areolar tissue, particularly the nodular lesions, have been separated as different from the diffuse process in the organs and

various explanations have been given for their occurrence. They have been regarded as tumors of the connective tissue secondarily infiltrated with lipoids; as special tumors developing from xanthoma cells; as granulomas developing from an inflammation of undetermined nature which had provoked a local fixation of the excess lipoids circulating in the blood; or, as granulomas that had become xanthelasmic as the result of a degenerative process which had liberated the constitutional lipoid locally. In my recent paper in the "Archives of Internal Medicine," I reviewed the literature and presented reasons for regarding this group of cases as a form of massive xanthomatosis, as it frequently occurs in early childhood. This condition representing lipoid cell hyperplasia of the reticulo-endothelial system and the pathologic change, diffuse and nodular, being the manifestation of a primary disturbance of the lipoid metabolism.

Local liberation of lipoid may cause the formation of cholesterin granulomas. Various inflammatory and suppurative processes, as well as mesenchymal tumors, can be complicated by lipoid infiltration. Because of the extent and similarity of the lesions found in Christian's syndrome, I regarded them all, both diffuse and nodular, as part of the same pathological condition. Trauma, toxic and infectious irritation may determine the localization, but these lesions are all manifestations of a primary disturbance in lipoid metabolism.

We are dealing with a pathological change, particularly involving the reticulo-endothelial system and resulting from abnormal or excess lipoids circulating in the body fluids, as is shown by vital staining and experimentation in the cholesterol feeding of animals. First of all, there is observed an increase of lipoids in the blood, then an infiltration of the tissues takes place. According to this hypothesis, the reticulo-endothelial system plays only a passive rôle. Infiltration occurs because the lipoids in the body fluids exceed a certain level.

There is nothing unusual about the topography of this disuse, all parts of the reticulo-endothelial system participate. Infiltration occurs in the reticular cells of certain organs and endothelial cells of blood and lymph vessels generally, and finally, extends over into the parenchymal cells of certain organs.

In rapid development the infiltration is diffuse. In slow development the change is more localized, assuming at times a tumor-like appearance. In the course of time, there is fibrosis, occasionally necrosis and cyst formation which mask the original picture.

In the same manner the chemical content of the cells varies. In Christian's syndrome, microchemical and chemical analysis shows these cells to contain cholesterol esters, phosphatid lipoid and neutral fats in varying proportions and amounts.

There has been a great deal of discussion as to why lipoids accumulate in the body fluids. Abnormal congenital predisposition has usually been ascribed to the infantile type of this disease, but this is not sufficient explanation. That disturbance of excretion may play a part seems probable. Herzenberg thought liver dysfunction

important in her case. It would seem that, superimposed upon a constitutional anomaly of lipoid metabolism, a disturbance of liver function and also of the lungs, which Aschoff regards as excretory organs for fats and lipoids, causes an excessive accumulation of lipoids in the body fluids accounting for the massive storage of lipoids observed in Christian's syndrome.

A certain number of lipoids are normal body constituents. They appear in the body physiologically and become more apparent in the retrogressive changes of old age. Kawamura says that they easily pass the normal point and become pathogenic.

This view, based on animal experimentation, has not been entirely accepted, because the experiments were done on herbivorous animals unaccustomed to fats and lipoids, but recently, Kawamura and Yuasa have confirmed the observations in omnivorae, and for that reason Yuasa believes that there is no longer any reason for not applying the experimental evidence to man.

*The Conditions that Should be Regarded as Primary Lipoid Cell Hyperplasias of the Reticulo-endothelium.* Ludwig Pick, to whom we are indebted for the foundation work in this study, separates, in his writings, the different lipoid cell hyperplasias of the reticulo-endothelial system, although in describing the form of the disease which occurs most frequently in infancy, he says that protracted type of this metabolic affection seems probable. In my paper in the "Archives of Internal Medicine," I expressed the opinion that Christian's syndrome represented a form of this disease which permitted bringing the different lipoid cell hyperplasias all into closer unity. At the same time, Herzenberg's report appeared describing a case of Christian's syndrome under the title "Die Skelettform der Niemann-Pickschen Krankheit," partly confirming this opinion and presenting for the first time evidence of the familial character of this syndrome, and there seems to be sufficient ground in the literature on xanthoma to consider most of the lipoid cell hyperplasias as a single disease, resulting from a primary constitutional, sometimes, familial deviation of lipoid metabolism.

The clinical conditions which can be bought together as lipoid cell hyperplasias, the result of a primary disturbance and of lipoid metabolism are: Niemann's disease, the rapidly developing syndrome of splenohepatomegaly occurring in infancy; Christian's syndrome, the characteristic skeletal form most often observed in early childhood; and Xanthoma in all the various forms described, for the most part, in the dermatological literature. These last will require further study from this point of view, to be properly brought into the grouping. Some of them will be found to be mild forms in the two preceding groups, and others will represent the adult types of this disease. There are transition cases from Niemann-Pick's syndrome to Christian's syndrome and on to the adult forms of xanthomatosis reported in the literature. (Fahr and Stamm, Oppenheimer and Fishberg, and others mentioned in my previous paper). In regard to the cases of xanthoma associated with icterus and diseases of the liver, and certain kid-

ney affections, these symptoms are secondary to the lipoid cell hyperplasia and also represent the manifestations of a primary disturbance in lipoid metabolism. The cases showing glycosuria and diabetes mellitus fall into the same grouping, only modified by a disturbance of carbohydrate metabolism, but it may be that the disturbance in carbohydrate metabolism in such cases, results from the lipoid cell hyperplasia, at least that the pathological change comes from a primary disturbance in lipoid metabolism.

As for Gaucher's disease, according to Ludwig Pick, it also represents a constitutional familial affection resulting from a primary disturbance of lipoid metabolism, but showing certain definite variations. In Gaucher's disease a complex lipoid, principally a sphingogalactocide-kerasin, is stored in the reticulum cells of the lymph-hemopoietic system, but limited to the spleen, liver, lymph nodes and bone marrow. In Niemann-Pick's syndrome the lipoid, especially a phosphatid, is stored in all parts of the lymph-hemopoietic system and no organ or tissues are immune to the deposits. As a result, the organs in Gaucher's contain large cells filled with a fibrillar protoplasm, resisting staining, quite different from the large vacuolated foamy cells in Niemann-Pick's syndrome.

In Christian's syndrome, the foamy cells contain phosphatids, but more cholesterol, anisotropic bodies and neutral fats, while in adult manifestations, usually cholesterin esters and anisotropic bodies, and sometimes, neutral fats predominate. The cells are like the cells found in Niemann-Pick's syndrome. Oppenheimer and Fishberg observed that "There are no essential differences, in cell morphology, between Niemann-Pick's disease and the other simple forms of lipoid cell hyperplasia," except, those that can be explained on the ground of the patient's general metabolic state, and as I suggested, in my previous paper, further investigation may determine that this is the only difference between Gaucher's and Niemann-Pick's disease.

In all these forms—the clinical manifestations, the anatomic and microscopic changes, and the chemical content of the lesions show great variations, but they represent the same irritative proliferation of connective elements, (i.e., reticulo-endothelial hyperplasia resulting from the infiltration of lipoids), their only difference being the nature of the lipoids concerned. The manifestations vary in clinical form according to the age of the patient, the rate of development, the intensity and the duration of the process.

Alpert, who suggests bringing all these different forms under the general head of Gaucher's disease, as familial affections due to one cause, but showing many different pictures, says "We must not be surprised that the histochemical and clinical types of Gaucher's disease multiply themselves. It is well to recognize and study these different types, but also it is well not to be troubled by their multiplication. It is natural because we are dealing essentially, with a familial disease of which, in spite of the different types, it is necessary to conserve the general unity."

It appears to me that from our pres-

ent knowledge of all these varied affections, we can place them in two clinical groups:

1. Gaucher's disease—with infantile, early childhood and adult forms well correlated.

2. Simple lipoid cell hyperplasias in which there is at present no unity—represented by Niemann's syndrome in infancy, Christian's syndrome occurring in early childhood, and the various types of xanthomatosis which appear in later life—representing the adult forms of this disease.

These affections are identical within their own groups, and all show many analogies, but also certain specific differences in cell morphology and the chemical content of the cell. They all represent the manifestations of a primary disturbance in lipoid metabolism, and on clinical grounds with the above reservations, should be grouped together.

It would seem appropriate to bring all the simple lipoid cell hyperplasias included in the second group under the general heading of Niemann-Pick's Disease. According to this interpretation, Niemann-Pick's disease would manifest itself; in infancy, particularly by spleno-hepatomegaly, extreme cachexia and nervous symptoms, and would be rapidly fatal; in childhood by skeletal defects, sometimes, splenohepatomegaly, exophthalmos, diabetes insipidus, dwarfism, dystrophia, adiposogenitalis, anemia, and would be a progressive disease which is frequently fatal in from two to four years; in adult life the symptoms would be more diversified and the course slower, and this disease would manifest itself either by splenohepatomegaly and diabetes mellitus, icterus and certain liver disorders, or kidney affections.

In conclusion, I believe I have described a remarkable pathological change—lipoid cell hyperplasia, a lipoid storage disease of the reticuloendothelial system—"lipoid gout." This change has been studied by pathologists for a long time, but its clinical importance is not generally recognized.

In my first paper, I discussed, particularly, the pathogenesis of this affection in its relation to xanthomatosis and mentioned the many conditions that are explained by such a pathologic change. I need not repeat them here, but this pathological change which affects all parts of the body should be of interest to the clinician and surgeon alike, as it suggests the manner of treatment.

## BIBLIOGRAPHY


Alpert, E.: La maladie de Gaucher. Les diversés variétés et particulierment ses variétés precoces, Bull. Méd., Paris, Jan. 1927.

Berkheiser, E. J.: Multiple Myelomas of Children, Arch. Surg. 8: 853 (May) 1924.

Bloom, W.: Splenomegaly (Type Gaucher) and lipoid histiocytosis (Type Niemann) Am. J. Path. 1: 595, 1925.

Bloom, W.: The histogenesis of essential lipoid histiocytosis (Niemann-Pick disease), Arch. Path. 6: 827, 1928.

Brahn, B., and Pick, L.: Zur chemischen organanalyse bei der Lipoidzelligen spleno-hepatomegalie typus Niemann Pick, Klin. Wchnschr. 6: 2367, 1927.

CHRISTIAN, H. A.: Defects in membranous bones, exophthalmos and diabetes insipidus; Contributions to medical and biological research, N. Y., Hoeber, 1919, vol. 1, p. 390.

CORCAN, P., OBERLING, C., and DIENST, G.: La maladie de Niemann-Pick, Rev. franc. de pédiat. 3: 789 (Dec.) 1927.

DANZER, B. S.: Defects in the membranous bones, diabetes insipidus and exophthalmos, Am. J. Dis. Child. 31: 480 (April) 1926.

FAHR, T., and STAMM, C.: Kurzer Beitrag zur Frage der Splenomegalie Typ. Gaucher, Monatschr. f. Kinderh. 26: 169, 1923.

FAHR, T., and STAMM, C.: Zur Frage der sogenannten Lipoidzellen-hyperplasie, Klin. Wchnschr. 3: 1206, 1924.

GRIFFITH, J. P. C.: Xanthoma tuberosum, with early jaundice and diabetes insipidus, Arch. Pediat. 39: 297 (May) 1922.

GROSH, L. C., and STIFEL, J. L.: Defects in membranous bones, diabetes insipidus and exophthalmos with a report of a case, Arch. Int. Med. 31: 76 (Jan.) 1923.

HAMBURGER, R.: Lipoidzellige Splenohepatomegalie (Typus Niemann-Pick) in Verbindung mit amaurotischer Idiotie bei einem 14 Monate alten Mädchen, Jahrb. f. Kinderh. 116: 41, May 13, 1927.

HAND, ALFRED: Defects of membranous bones, exophthalmos and polyuria in childhood—Is it dyspituitarism? Am. J. M. Sc. 162: 509, 1921.

HERZENBERG, HELENE: Die Skelettform der Niemann-Pickschen Krankheit, Virchows Arch. f. path. Anat. 269: 614, 1928.

KAWAMURA, R.: Neue beiträge zur Morphologie und Physiologie der Cholesterinsteatose, Jena, Fischer, 1927.

KAY, T. W.: Acquired hydrocephalus with atrophic bone changes, exophthalmos and polyuria, Penn. M. J. 9: 520, 1905-1906.

KYRKLUND, R.: Beitrag zu einem seltenen Symptomenkomplex (Schädelerweichungen, Exophthalmus Dystrophia adiposo genitalis, Diabetes insipidus), Ztschr. f. Kinderh. 46: 56, 1926.

LÉVY, G.: Xanthélasma et xanthome, Ann. d'anat. path. méd.-chir., 2: 247-282, 1925.

LUBARSCH, O.: Bemerkungen zu der Arbeit H. Herzenbergs über die Skelettform der Niemann-Pickschen Krankheit, Virchows Arch. f. path. Anat. 269: 823, 1928.

OBERLING, C.: Gaucher's Disease, Ann. d'anat. path. 3: 353, 1926.

OPPENHEIMER, B. S., and FISHBERG, A. M.: Lipemia and reticulo-endothelial apparatus, Arch. Int. Med. 36: 667 (Nov.) 1925.

PICK, LUDWIG: Beiträge zur Kenntnis des Morbus Gaucher der Säuglinge und der Beteiligung des Skelettsystems, Med. Klinik. 21: 441, 475, 509, 667, 1925.

PICK, LUDWIG: Die Histio- und Pathogenese des Morbus Gaucher, seine histio- und pathogenetische Abgrenzung von ähnlichen Krankheitszuständen, insbesondere der lipoidzelligen Splenohepatomegalie (Typus Niemann), Med. Klinik, 20: 1526, 1924.

PICK, LUDWIG: Der Morbus Gaucher und die ihm ähnlichen Erkrankungen, Ergbn. d. inn. med. u. Kinderh. 29: 519, 1926.

PICK, LUDWIG: Die skelettform (ossuäre Form) des Morbus Gaucher, Jena. Fischer, 1927.

PICK, L., and BIELSCHOWSKY, M.: Über lipoidzellige Splenomegalie (Typus Niemann-Pick) und amaurotische Idiotie, Klin. Wchnschr. 6: 1631, 1927.

PICK, LUDWIG: Über die lipoidzellige Splenohepotomegalie Typus Niemann-Pick als Stoffwechseler-krankung, Med. Klin. 23: 1483 (Sept.) 1927.)

PICK, LUDWIG: Über lipoidzellige Splenohepatomegalie, Varhandl. d. Gesellsch. f. Verdauungs—und Stoffwechselkrankheiten, v. 8, Sept. 14, 1928.

PUSEY, W. A., and JOHNSTONE, O. P.: A case of Xanthoma diabeticorum and lipoma multiplex and a case of Xanthoma approaching the diabetic type with diabetes insipidus, J. Cutan. Dis. 26: 552, 1908.

ROWLAND, R. S.: Xanthomatosis and the reticulo-endothelial system, Arch. Int. Med. 42: 611 (Nov.) 1928.

SCHÜLLER, ARTUR: Ueber eigenartige Schädeldefekte im Jugendalter, Fortschr. a.d. Geb. d.Roentgenstrahlen. 23: 12, 1915-1916.

SCHÜLLER, ARTUR: Ueber ein eigenartiges syndrom von Dyspituitarismus, Wien. Med. Wchnschr. 71: 510, 1921.

SCHULZ, A., WERMBTER, F., and PUHL, H.: Eigentümliche granulomartige Systemerkrankung des hämatopoetischen Apparates (Hyperplasie des retikuloendothelialen Apparates), Virchow's Arch. f. path. Anat. 252: 519, 1924.

STOWE, W. R.: Case of diabetes insipidus associated with defects in skull, M. J. Australia (Supp. 5) pp. 144-146, Sept. 10, 1927.

THOMPSON, C. Q., KEEGAN, J. J., and DUNN, A. D.: Defects of membranous bones, exophthalmos and diabetes insipidus, Arch. int. Med. 36: 650 (Nov.) 1925.

WEIDMAN, F. D., and FREEMAN, W.: Xanthoma tuberosum: Two necropsies disclosing lesions of central nervous system and other tissues, Arch. Dermat. & Syph. 9: 149 (Feb.) 1924.

WELT, SARAH, ROSENTHAL, NATHAN, and OPPENHEIMER, B. S.: Gaucher's splenomegaly, J. A. M. A. 92: 637 (Feb.) 1929.

YUASA, D.: Über die experimentelle cholesterinkrankheit bei Omnivoren, Beitr. z. path. Anat. u. z. allg. Path. 80: 570, 1928.

# The Ketogenic Diet in the Treatment of Epilepsy

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EPILEPSY is a symptom-complex consisting of sudden periodic loss of consciousness, convulsive movements or both. Of the same nature are certain other phenomena referred to as epileptic equivelants, such as migraine, certain cases of periodic vertigo, periodic voracity, dipsomania and other periodic mental disorders. Epilepsy is thus a periodic reaction of the nervous system, in which various motor, sensory, visceral and psychic syndromes may occur. Levy and Patrick (1) have recently described a number of so-called pre-epileptic phenomena, which may antedate the major seizure for many years; these consist of minor, but sudden and periodic symptoms, such as pallor of the face, sense of thirst or of asphyxia, trembling, staggering, screaming, hot flushes and other disorders of momentary duration. Recognition of these early phenomena is important, as it is in the earliest stages that treatment is most beneficial. The public should be taught the significance of such symptoms. It has been estimated that there are about 500,000 epileptics in the United States. The situation demands the attention of the medical profession, in order that progress be made in our knowledge of this condition, and that patients be treated as early as possible.

By definition, epilepsy is not a disease, but a symptom-complex or syndrome. To emphasize this, it has been proposed to discard the term epilepsy, and to speak of these conditions as paroxysmal disorders. There is no need to discard the term epilepsy if it be properly understood. It is not per se a malignant condition, neither hopeless of cure, nor ending in dementia. When dementia does occur, it is not dependent upon the severity or frequency of seizures, but is due to the cause behind the attacks. Mental deficiency is present in only about 4 % of cases. Epilepsy should be looked upon as any other symptom, such as headache. The one difference from other symptoms is the fact that each seizure constitutes a severe injury to the brain, producing changes which may in turn incite attacks. This may explain the marked tendency for seizures to recur, what is termed the epileptic habit. This vicious circle must be interrupted by treatment as early as possible.

Epilepsy is associated with many conditions. It may be said that either an organic lesion or a functional disturbance in the brain must be present

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in all cases. A vascular spasm is apparently the immediate precursor of the attack. No other fundamental factor common to all cases has been found. Some of the conditions known to be associated with convulsions are the following:

1. Organic disease of the brain; any disease of the brain may be accompanied by repeated convulsions. These may be listed as congenital brain disease, heredo-degenerations, brain trauma, tumor, parasitic cysts, syphilis, tuberculosis, meningitis, abscess, cerebral edema, epidemic encephalitis, encephalitis and cerebral palsy of childhood, progressive subcortical degeneration, multiple sclerosis, presenile gliosis and senile cortical atrophy.

2. Circulatory disorders; these include vascular anomalies of the brain, cerebral aneurism, cerebral arteriosclerosis and endarteritis, angioma, vascular spams (Raynaud's), heart block, paroxysmal tachycardia and blood dyscrasias. Convulsions may also occur in cerebral embolism, thrombosis and hemorrhage.

3. Intoxications. These may be exogenous, as chronic alcoholism, lead poisoning, cocaine, absinthe or after injection of insulin. Protein sensitization may be a factor in some cases. Endogenous intoxications also cause convulsions as in eclampsia, uremia, endocrine disorders, intestinal toxemia, and disturbance of acid-base relationship (hyperventilation).

4. Psychic conflicts.

5. Reflex disorders. Although reflex disorders occupied a prominent place in the etiology of epilepsy by the older writers, it is doubtful if such is ever a true cause of epilepsy. A case reported by Block (2) suggests that reflex epilepsy occurs only in association with organic disease of the brain.

Lennox and Cobb (3) have made a critical analysis of the etiologic factors of epilepsy. They believe that there are possibly three factors involved in every case: A. Pathological changes in the nervous system. It is doubtful if the brain of any epileptic is normal, although there has been little opportunity to study the brain in early cases. If normal at the start, secondary changes probably develop, increasing with time, unless the seizures be controlled. The rarity of epilepsy in cases of known disease of the brain however, suggests an additional factor. B. Functional instability of the nerve cells. This may be based on a hereditary tendency (about which little is known), psychic conflicts, or more probably on complex physico-chemical changes within the cells. Among the latter, one must consider such changes as anoxemia, ionic and colloidal disturbances, change in hydrogen-ion concentration, edema and changes in cellular permeability. C. Extracerebral disorders, which influence the function of the brain. Among these, are disturbances of intracranial circulation, of the autonomic nervous system, metabolism, the endocrines, respiration and the gastrointestinal tract.

The importance of the above three factors would vary in individual cases, and at different times in any given case. The analysis of the etiologic factors in a particular case is often

difficult. The initial precipitating factors may have ceased to be important, or the attacks may be a manifestation of an otherwise asymptomatic brain disease. Epilepsy may be the sole evidence of a brain tumor or of multiple sclerosis for years before other signs appear. According to Cobb, the immediate cause of a seizure may be conceived of as a vascular spasm of the brain, leading to deficient oxygenation of the nerve cells, intracellular alkalosis, electrolytic changes and edema, these being associated with increased irritability to the point of sudden discharges of nervous impulses. The apnea and muscular contractions of the attack lead to an accumulation of carbon-dioxide and lactic acid in the tissues, which reverse the metabolic disorder, and the attack then ceases.

The first principle in the treatment of epilepsy is a thorough search for the etiologic factors. The history must be carefully investigated with respect to familial nervous disorders, birth and development of the patient, nutritional disorders of childhood, food idiosyncracies, previous infectious diseases and head injuries. A thorough neurological examination should be made and repeated at intervals. This should include a roentgen-ray of the head and spinal fluid examination with measurement of the cerebro-spinal fluid pressure. In certain cases, a ventriculogram, or encephalogram (made by injection of air through a lumbar puncture) is indicated. Physical examination must be complete, with special attention to anomalies, endocrine disorders, foci of infection, and the circulatory system. Laboratory examination should include in addition to the spinal fluid examination, study of the blood, urine and stools. In certain cases, basal metabolism, protein sensitization tests and a roentgen-ray examination of the gastro-intestinal tract may be of value. The Wassermann test should never be neglected. Other examinations may be indicated in certain cases. Some investigation of the psychic life of the patient should be made in all cases. Frequently however, all these examinations will reveal little that seems significant.

The second principle of treatment is that the attacks must be stopped as soon as possible, as they tend to recur. Cure of epilepsy is possible only by prevention of attacks for a long period of time. To correct the suspected etiological factors, without giving symptomatic treatment may result in failure. Regardless of the etiology, all cases should receive symptomatic treatment. This is true even in cases of brain tumor, where such treatment may not be necessary for very long, but should be given for a time after operation. The practice of allowing patients to have repeated seizures for a long time without treatment, because of hesitation in diagnosis cannot be too strongly condemned. Convulsions tend to recur, and convulsions from any cause may become epilepsy.

In each case, attention must be paid to all possible etiologic factors. Surgical treatment may be indicated as in cases of brain tumor, abscess, arachnoid cysts or depressed bone. Nonspecific protein treatment or desensitization may be indicated in a few cases. Endocrine disorders may indicate glandular therapy. The patient

should always be placed in the best possible physical condition. In regard to general hygiene, avoidance of alcohol, sexual excess, physical and mental exhaustion and attention to correct eating habits and intestinal elimination are recommended in all cases. Muskens (4) places first emphasis on hygienic methods, while Collier (5) states that he has seen no particular value in them. Psychotherapy is a valuable adjunct in all cases. Among the drugs, bromides have always occupied first place. Although much abused, today we are able to administer bromides scientifically, due to the work of Ulrich (6) and others. The action of bromides is dependent upon the relation to chlorides in the body; in order to obtain therapeutic action as well as to avoid bromide intoxication, this bromide-chloride ratio must be kept within certain limits. There must be a proportionate intake of both salts. Wuth (7) has devised a method for estimation of the bromide content of the blood which is of aid in regulation of the dosage. Because of ease of administration, luminal has largely displaced bromides; unfortunately, it is often inadequate for minor seizures. Potassium boricotartrate is another drug of value, but less effective (8). Other drugs may be indicated in specific cases.

Diet has always received attention in the treatment of epilepsy. Various diets have been advocated on an empirical basis. Low protein diets have been used although biochemical investigations have shown no disorder of protein metabolism. Saltfree diets have been of value in association with the use of bromides. Low carbohydrate diets have been used in accordance with the hypothesis of Cuneo (9) that there is a faulty intestinal digestion of carbohydrates. Many other diets have been proposed.

The ketogenic diet has been developed on a more rational basis. No one denies its beneficial effect in certain cases. Although some state that its effect is due to elimination of foods to which the patient is sensitized, or to regularity in eating, these views cannot be upheld. The diet was developed on the basis of the effect of starvation. Fasting was used years ago in epilepsy as in other diseases. Conklin (10) an osteopathic practitioner was the first to use it extensively and reported remarkable results. In 1921, Geyelin (11) reported on 26 cases, starved for 20 days; attacks ceased in 16 cases, and in 2 did not return within a year. Lennox and Cobb (12) have recently reported on 27 cases, starved for 4-21 days; attacks ceased in 10, and 10 others were improved. Fasting has but temporary results, the attacks usually recurring at the end of the fast.

As fasting cannot be prolonged, and as similar bio-chemical changes may be produced by a ketogenic diet, Wilder (13) in 1921 proposed treating epilepsy with a ketogenic diet, a low carbohydrate- high fat diet such that a ketosis is produced and maintained. The ketosis is shown by the marked increase in ketone bodies in the blood, urine and alveolar air: there is also produced a marked rise in uric acid in the blood, slight fall in pH of the blood, slight fall in carbon-dioxide combining power of the blood and a change in carbohydrate metabolism; the fasting blood sugar is low, and the

glucose tolerance curve shows a delayed rise, higher than normal, with a delayed fall. Non-protein nitrogen, calcium, phosphorus and chlorides show no change (14).

There are many reports in the literature tending to show that at least a group of epileptics show a wide variation from hour to hour and day to day in the hydrogen-ion concentration of the blood and urine, although within normal limits; preceding attacks, there is a tendency toward an alkalosis, and following attacks there is a temporary acidosis. It has been shown that a sudden shift from an acidosis to an alkalosis by the administration of alkali may increase the frequency of seizures (3); the same result occurs with hyperventilation. This may be compared with the muscular cramps of tetany, produced by over-dosage of alkali. It has also been found that carbon-dioxide, as in rebreathing, stops epileptic attacks as well as persistent hiccup and other muscular spasms. In addition to the change in hydrogen-ion concentration, anoxemia and electrolytic changes are probably important. Acidosis produced by the administration of acid-forming salts is only of temporary benefit; Lennox and Cobb believe this is due to electrolytic changes which counter-act the acidosis, while Peterman (15) believes this shows that acidosis is not the essential factor. Peterman believes that the diet is beneficial because of a sedative action of the ketone bodies on the nerve cells; Lennox and Cobb believe that the diet induces complex physico-chemical changes within the nerve cells, among which a change in the hydrogen-ion concentration is an important item. Further work is needed to fully explain the action of the diet. What effect the change in carbohydrate metabolism, or the increase in uric acid in the blood may have is uncertain.

The use of this diet has been more successful in children than in adults because it is easier to produce and maintain a ketosis in children than it is in adults. No harmful results have occurred and children have been maintained on the diet through such diseases as whooping cough, scarlet fever and measles. What might develop from the use of this diet over a period of years is not known. Fortunately in many cases, the diet need not be used over a very long period of time. It is sometimes possible after freedom from attacks for some months, to gradually revert to a normal diet without recurrence of attacks. There are cases reported in which attacks have not occurred for as long as 3-4 years after resumption of a normal diet.

The results obtained by the ketogenic diet vary. Little improvement is to be expected in cases of long duration, or marked mental deterioration or of gross organic disease of the brain. In certain cases, the attacks cease and do not return after gradual resumption of a normal diet. In others, the attacks reappear on any change in diet. In some cases, the diet has to be supplemented with a sedative drug. Likewise certain cases treated with drugs will do better with the addition of the ketogenic diet. Some cases receive no benefit from the diet. Some benefit may be obtained in certain cases with brain pathology, as in encephalitis or cerebral palsy of childhood. That adults may also receive benefit is shown

by the report of Barborka (16); he stated that of 32 cases, attacks ceased in 7 and diminished in frequency in 12. It is impossible to predict whether a patient will be benefited or not. The most favorable cases are those of short duration in children without evidence of brain disease or of mental deficiency. Talbott (17) reported marked benefit in 30% of such selected cases. Helmholtz (18) after five years experience reported cessation of attacks in 31% and marked benefit in 23%, or good results in 54% of cases. The diet seems particularly beneficial in cases of frequent petit mal, in which luminal is often ineffective. Peterman has reported that 20 of his cases are now on a normal diet and have been free of attacks from 6 months to 3 years. The improvement obtained seems definitely proportional to the degree of ketosis developed. In view of such results, the ketogenic diet must be accepted as a valuable addition to the treatment of certain cases of epilepsy.

The diet must contain the caloric requirements of the individual according to their age, weight and height. It must also contain the protein requirement, which may be accepted as 2/3 grams per kilogram body weight for adults, and 1 gram per kilogram body weight for children. The carbohydrate and fat are then adjusted according to well known principles as to produce a ketosis. The ketogenic ratio (relation of fatty acids to dextrose produced) must exceed 2, and frequently a ratio of 3 or 4 may be necessary. Vitamines are to be supplied, as in fats, green vegetables, cream and eggs. Palatability must be given attention. There is no limitation of salts. In some cases the diet must be supplemented with inert material to avoid hunger. As the diet tends to induce constipation, attention must be given to this matter. The patients must be intelligent and cooperative. Both children and adults take the diet readily when willing to cooperate. It is often difficult to get cooperation, as patients state that have tried various diets without benefit, or that they do not have indigestion. It is thus necessary to explain the purpose of the diet at the start. Urinalysis must be done at frequent intervals in order to regulate the diet so as to obtain a ketosis of sufficient degree. Patients may be taught how to test the urine, and sometimes this is of aid in maintaining their interest. Simple methods of calculating the diet have been devised by McQuarrie and Keith (19) for children and by Barborka (16) for adults. It is usually best to begin with a 2-3 day fast, but this is not always necessary. It has been my practice to give small doses of luminal until a ketosis is developed, and then to withdraw it if possible.

It is not my intention at this time to report any further statistics. Some examples of the response to the diet are briefly reported:

*Case* 1. A colored girl, aged 16 yrs. was first seen in April 1927. Generalized attacks had been occurring from one to three times a month for two years. She stated that she had taken drugs with little benefit. The usual clinical investigations did not reveal the cause of the attacks. She was placed on a ketogenic diet, and had no further attacks from the start of the diet. One year later, no attacks having occurred within this time, she voluntarily abruptly broke the diet. She continued free of at-

tacks for five months longer, when she again had a seizure. She was again placed on the diet, and has been free of attacks. No other medication was given during the treatment.

This case represents a very favorable effect of the diet. It is possible if the change to a normal diet had been more gradual, the attack would not have occurred five months later. While it may not be possible to bring her back to a normal diet, evidently the diet will control her attacks whenever necessary. That the diet is superior in this case to proper drug treatment cannot be said, but that it is effective cannot be denied.

*Case 2.* A white male, aged 18 yrs. was first seen in September 1927. He had been having 3-4 major convulsions a year and frequent petit mal attacks since the age of 4 years. The usual investigations revealed little; there was a family history of migraine. He was placed on a ketogenic diet, and remained free of attacks for five months, when he broke his diet, and had another seizure. He would not cooperate with further dietary treatment.

In this case also, the diet seemed to have a definite beneficial effect, although it may not have been possible to revert to a normal diet without return of seizures.

*Case 3.* A child of 6 yrs. was first seen in May 1927. She gave a history of high fever and convulsions, followed by a left hemiplegia at the age of 15 months. Convulsions had continued from that time, Jacksonian in type, and occurring once a week to several times daily. A diagnosis of encephalitis or cerebral palsy of childhood was made. She was placed on a ketogenic diet and small doses of luminal, which she was taking when seen. With the addition of dietary treatment, there has been a marked diminution in frequency of attacks. The interval between attacks is now frequently as long as six weeks. In addition there has been an increased mental alertness, with decreased irritability.

This case represents a type in which it is believed that the addition of the ketogenic diet to drug treatment gives better results than either alone. By such combined treatment, one may be able to avoid the high dosage of drugs sometimes necessary.

*Case 4.* A child of 3 years was first seen in February 1928. The child presented a marked precocious development or pubertas praecox. No definite basis was found for the precocious puberty after thorough study, including a craniotomy with exposure of the pineal region. The neurological and other examinations gave no abnormal findings except the precocious development. This child had frequent petit mal attacks, in spite of the administration of luminal, at least 3-4 times daily. After beginning the diet he went a week without any attacks being observed. This improvement has continued under combined treatment. Withdrawal of the luminal (¼ grain twice daily) or a break in the diet results in increased frequency of seizures. Under combined treatment, attacks never occur more than once daily, and at intervals of 3-6 days.

In this case, it is also felt that combined treatment gives better results than either alone.

*Case 5.* A young man aged 22 yrs. was first seen in January 1928. He had had generalized convulsions from the ages of one to seven years, and petit mal attacks beginning at the age of 16 years. These attacks occurred about 10-12 times monthly. He had been treated with luminal without benefit. He was placed on a ketogenic diet, and in spite of a marked ketosis being maintained for 8 weeks, showed no improvement. The early onset, and history of long dry labor, suggested that a birth injury was probably the cause of the attacks in this case.

This case represents a type in which no improvement was obtained by the ketogenic diet after two months. It is possible that the long duration of the attacks and probable organic changes in the brain were responsible for the lack of improvement.

## Summary

Epilepsy is a syndrome which may be associated with many conditions.

Rational treatment should include first a thorough search for etiologic factors in each particular case. Regardless of etiology however, an effort must be made to stop the attacks so that the vicious circle known as the epileptic habit does not develop. Such symptomatic treatment should be given as early as possible. Luminal and bromides are the two drugs of choice in symptomatic treatment. The ketogenic diet represents an addition to these methods, which has a more rational basis than other diets proposed. It is not to be considered as a cure-all, but the evidence indicates that it must be accepted as a valuable aid in certain cases. Its exact place in the treatment of epilepsy, as well as a full explanation of its action remain to be determined.

## REFERENCES


(1) Levy, D. M., and Patrick, H.: Recurrent 'attacks' Other Than Migraine and Infantile Convulsions Preceding 'True' Epilepsy. Arch. Neurol. and Psychiat. *20*: 443. Sept. 1928.

(2) Block, E. B.: Epilepsy and Organic Brain Disease." Ann. Int. Med. *2*: 531. Dec. 1928.

(3) Lennox, W. G. and Cobb, S.: Epilepsy. Medicine *7*: 105. May 1928.

(4) Muskens, L. J. J.: Epilepsy.—Comparative Pathogenesis, Symptoms, Treatment. Wm. Wood and Co. New York. 1928.

(5) Collier, J.: Epilepsy. Lumleian Lectures. Lancet 1: 687. April 7, 1928.

(6) Ulrich, A.: The Bromide-Chloride Treatment of Epilepsy. Med. J. and Rec. *126*: 1, 41. July 4, 1927.

(7) Wuth, O.: Rational Bromide Treatment: New Methods of its Control. J. A. M. A. 88: 2013. June 25, 1927.

(8) Lennox, W. G. and Wright, L. H.: Comparative Effects of Borotartrate and of Luminal in Seizures of Epilepsy. Dec. *23*, 1926. Bost. Med. and Surg. Journ. 195: 1195.

(9) Cuneo, G.: Studi sulla patogenes dell epilessia. La genesi dell' albumosoluria epilettica a la digestione intestinale dell proteine, degli idrati di Carbonio e dei grassi. Note e riv. di. psichiat. 14: 381, Sept.-Dec. 1926.

(10) Conklin, H. W.: The Cause and Treatment of Epilepsy. J. Am. Osteo. Ass'n. *22*: 11. Sept. 1922.

(11) Gevelin, H. R.: Fasting as a Method of Treating Epilepsy. Med. Rec. *99*: 1037. June 11, 1921.

(12) Lennox, W. G. and Cobb, S.: Studies in Epilepsy. viii- The Clinical Effect of Fasting. Arch. Neurol. and Psychiat. 20: 771. Oct. 1928.

(13) Wilder, R. M.: The Effect of Ketonuria on the Course of Epilepsy. Bull. Mayo Clinic *2*: 307. 1921.

(14) Talbot, J. F., Metcalf, K. M., and Moriarty, M.: Epilepsy—Chemical Investigations of Rational Treatment by Production of Ketosis. Am. J. Dis. Child. 33: 218. Feb. 1927.

Kohn, J. L., Fries, M. E. and Felshin, G.: Spontaneous and Induced Ketosis in Children. Effect on the Glucose Tolerance Test. Arch. Dis. Child. 34: 857. Nov. 1927.

Shaw, E. B. and Moriarty, M.: Hypoglycemia and Acidosis in Fasting Children with Idiopathic Epilepsy. Arch. Dis. Child. *28*: 553. Nov. 1924.

Hoeffe, G. and Moriarty, M.: The Effect of Fasting on the Metabolism of Epileptic Children. Arch. Dis. Child. *28*: 16. July, 1924.

Lennox, W. G.: Increase of Uric Acid in the Blood During Prolonged Starvation. J. A. M. A. *82*: 602. Feb. *23*, 1924.

(15) Peterman, M. G.: The Ketogenic Diet. J. A. M. A. 90: 1427. May 5, 1928.

(16) Barborka, C. J.: The Ketogenic Diet Treatment of Epilepsy in Adults. J. A. M. A. 91: 73. July 14, 1928.

(17) See footnote 14.

(18) Helmholtz, H. F.: The Treatment of Epilepsy in Childhood. J. A. M. A. 88: 2028. June 25, 1927.

(19) McQuarrie, J. and Keith, H. M.: Epilepsy in Children. Relationship of Variations in the Degree of Ketonuria to Occurrence of Convulsions in Children on Ketogenic Diets. Arch. Dis. Child. 34: 1013. Dec. 1927.

# Diffuse Scleroderma, With Case Report and Autopsy Findings*

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SCLERODERMA is a rare disease in the experience of any one observer. This is especially true of the diffuse form of the disease. Osler (1) did not see his first case until 1891; during the fourteen year period from 1891 to 1905 he saw a total of only twenty cases of scleroderma of all types (2): While the disease is said to be relatively more frequent in the United States than in other countries, Lewin and Heller (3) were able to list but thirty-two cases as having been reported from the North American continent, out of a total of 451 cases available for study of geographical distribution. Allbutt (4) gives the American incidence as 2 in 16,863. Hebra (5) never saw a single case. Out of a total of 7000 patients at his Berlin Clinic for nervous and mental diseases, Oppenheim (6) had only 7 cases of scleroderma. Since Watson (7) first described Curcia's case in 1754, there is mention of only some seven hundred cases in the literature.

Scleroderma has been recognized as a definite disease entity ever since Thirial's (8) paper (1854). Observation during the past century and a half has convinced numerous observers that scleroderma is indeed an entity, despite the various distinct clinical types (Sequeira (9), Stelwagon (10), MacLeod (11), Schamberg (12), Castle (13), Osler (2), Robinson (14), Lewin and Heller (3), et al). Crocker (15) classifies the disease into three groups: (1) Diffuse symmetrical scleroderma: (2) diffuse circumscribed, usually unsymmetrical scleroderma (morphoea); and (3) diffuse unsymmetrical scleroderma. He inclined to the opinion that the sclerema of infancy might be a separate, albeit related condition. Stelwagon (10) simply classifies it into the diffuse and circumscribed forms.

While there is much clinical evidence to agree with the above authorities, a study of the literature reveals that there has been unncessary confusion regarding nomenclature. Analysis of some of the cases reported as conforming to the criteria of Herxheimer and Hartman (16) for the diagnosis of acrodermatitis chronica atrophicans, raises a serious question as to the correctness of such an interpretation (Kingsbury (17), Kanoky and Sutton (18), and Robinson (14)). Many of the cases have been characterized by signs common to both conditions. For this reason and because

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of paucity of descriptive exactitude in some others, any attempt to tabulate the relative frequency of the diffuse and localized forms of the disease is foredoomed to failure. And if we accept the inherent unity of the various clinical forms of the disease, such a labor would not be fruitful of a great deal of light on the pathogenesis of this curious disease.

The literature contains much of fancy and little of fact to help us towards a better understanding of the etiology of scleroderma. Lewin and Heller (3) viewed the disease as an angioneurosis, a trophoneurosis or an angiotrophoneurosis. The origin of the disease in some obscure nervous or trophic lesion has since received wide endorsement (Cockayne (19), Crocker (15), Jacquet (20), Steven (21), Josephovitch (22), Stelwagon (10), et al). Williams (23) recently presented a patient with undoubted involvement of the nervous system. His case, however, presented some unusual features. It is not strange that the nervous system should be affected in the course of a disease showing such an extensive fibrosis of the internal organs as does scleroderma. For the most part the authors who favor involvement of the central nervous system as explanatory of the clinical manifestations of the disease, are able to cite little more than circumstantial evidence in support of their views. To credit a disease with such definite local pathological and clinical manifestations as due to a trophic disturbance fails to offer a concrete basis for the fuller understanding of the disease.

The thyroid gland has been implicated by numerous observers (Hektoen (24), Uhlenhuth (25), Samouilson (26), Graham Little (27)). Graham Little's report is of especial interest. His patient was operated upon by Kocher for the purpose of a homoioplastic thyroid graft into the tibia in 1911 and again eight months later in 1912. There was definite improvement of the sclerodermatous condition on both occasions. But in 1913, when again consulted, Kocher advised against a third implantation and contented himself with administration of the gland extract. The graft, therefore, failed of effecting a cure—the possibility of absorption of the graft has to be kept in mind, of course. This patient, moreover, showed an equally marked retrogression of the skin manifestations subsequent to the removal of some carious teeth. It is further worthy of note that Graham Little's patient had at various times exhibited signs and symptoms of overactivity as well as of underactivity of the thyroid gland.

Hektoen (24) presented details of a case of scleroderma coming to autopsy with a significant reduction in the iodine content of the thyroid gland, as determined by chemical analysis. His patient also showed an hyperplasia of the chromophilic cells of the pituitary gland—possibly a compensatory phenomenon. It is by no means unlikely, however, that the thyroid alteration in his patient was incidental to rather than causative of the scleroderma.

Sequeira (28) described four cases associated with Graves' disease. He concluded, however, that "It is true that a certain proportion of the cases are associated with affections of this

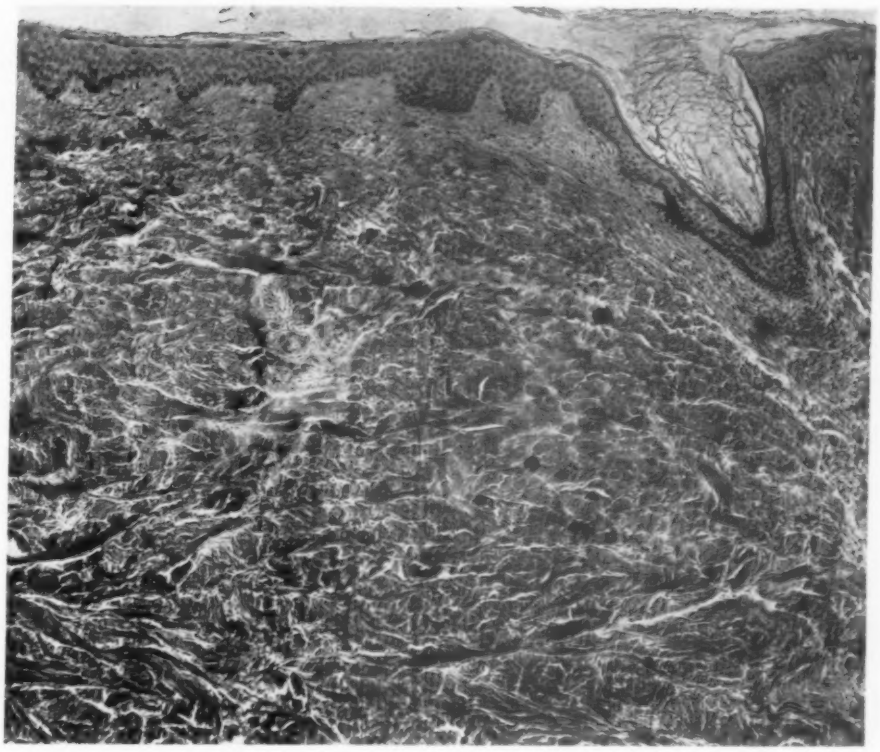

FIG. 1. Low power view of skin, showing hyaline fibrosis of corium, and atrophy of skin structures.

gland (thyroid) but there is nothing to warrant the conclusion that alterations in the activity of the gland or of its secretion are actually causative of scleroderma.

Osler (1) was unable to convince himself of any specific action of thyroid extract feeding on the sclerodermatous state, nor was he able to report definite improvement in his patients as the result of such medication.

Castle (13) has carefully reviewed the literature on this subject. He favors the view that the disease is of combined endocrine and nervous origin but refuses to implicate any one gland. He favors the concept that failure of any one of the endocrine organs may so disorganize the harmonious interplay of the glandular secretions as to evoke this rare syndrome.

The case presently to be reported may, on superficial analysis, be cited as further evidence in favor of the thyroidal origin of the disease. But a more careful scrutiny of the facts reveals that the changes noted in the thyroid were not in any way specific, but merely such as accompanied the stroma increase of the other organs.

The very frequency of thyroid disease and the relative and absolute rarity of scleroderma are almost prima

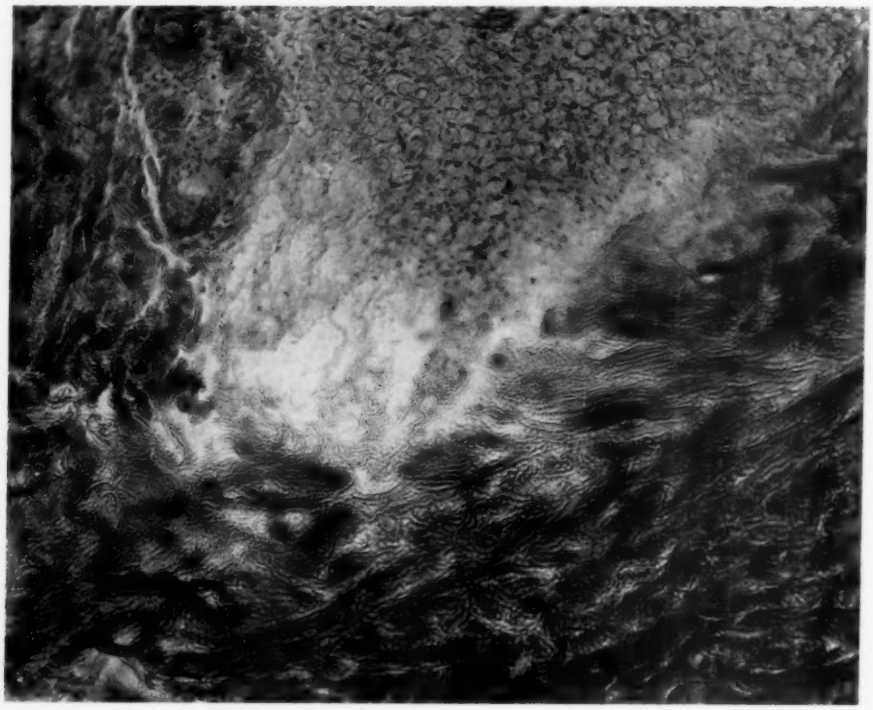

FIG. 2. Hyaline fibrosis of subcutaneous tissue. Atrophy of adipose tissue.

facie evidence against acceptance of the thyroid etiology.

That a disease as frequently accompanied by pigmentary changes as is scleroderma should be coupled with possible supra-renal disease is not surprising.

Lewin and Heller (3) collected 144 cases in their series of 508, showing an increase in pigment. Schultz (29) reported the case of a girl with scleroderma of the arms and legs, accompanied by pigmentation of the face and neck and by muscular atrophy. The disease ran a rapid course and terminated fatally four months after onset. At autopsy the left supra-renal gland was found to be increased in size, adherent to adjacent structures and to present a few small grey nodules. He failed to present a detailed histological description of sections of the gland, thereby materially detracting from the value of his observations.

Winfield (30) described a case simulating Addison's and Raynaud's disease, with marked benefit from administration of supra-renal extract. A second case coming under the care of the same author showed equally marked improvement under similar therapy. This aspect of the subject is well covered by Castle (13).

In our case the adrenals also showed some changes. Yet the clinical manifestations were not indicative of severe adrenal disease. It is not unlikely that adrenal changes may be responsible

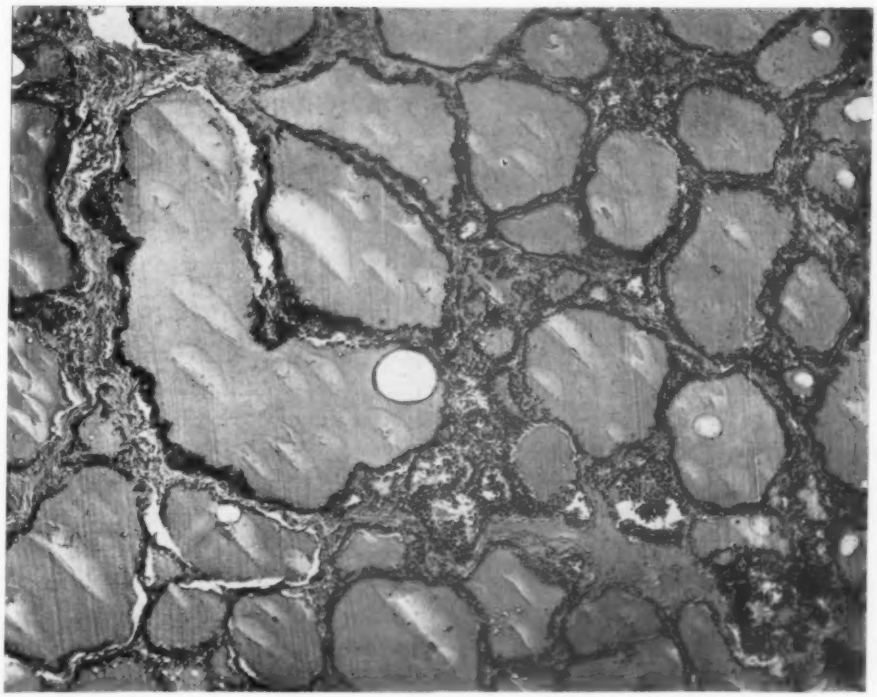

FIG. 3. Thyroid. Abundant colloid and slight fibrosis.

for the pigmentary changes and that seems a more logical, if conservative, view than implication of these organs as the basis for all the sclerodermatous changes.

Among other etiological considerations, the possibility of a syphilitic basis for this disease has been propounded (Schamberg (12), Jackson (31), Whitehouse (32), et al). Here the same objection as was raised in regard to thyroid disease holds good. Not unlikely, scleroderma has at times been manifested in demonstrably luetic patients. But we must be cautious in evaluating the significance of such a relationship. Syphilis is on the increase, scleroderma is not; scleroderma is at most only a very rare accompaniment of syphilis.

Ayres (33) has recently raised a question as to the possibility of arsenic poisoning being responsible for scleroderma. He cites cases in which he was able to demonstrate arsenic in the urine. But he admits that such a finding is not unusual in apparently healthy controls. In view, also, of the increased incidence of arsenical medication it would not be illogical to expect an increased incidence of scleroderma. Ayres urges histochemical investigation of the tissues but this is not a practicable plan (Weller (34)). Bramwell (35) reported nine cases, all males, in whom the scleroderma started in the hands, apparently from the use of cold chisels. Sequeira (36) reported the case of a youth who bruised himself severely across the

lower left chest and six months later noticed increased pigmentation over the area. At a later date he developed an extensive morphoea over this area. Roberts (37) also reported a case in which trauma was considered the immediate cause of morphoea. Fox (38) showed a case of morphoea guttata before the Dermatological Section of the Royal Society of Medicine in a woman who had been sunburnt. The lesion appeared over the sites of the blisters raised by the sunburn. Bancroft (39) reported the case of a girl who developed scleroderma and in whose blood he was able to demonstrate the presence of filariae.

Wolf and Vallette (40) have recently attempted to show that scleroderma is related to a disorder of the calcium and phosphorus metabolism. They present the detailed report of a patient with localized deposits of calcium at the edges of the sclerodermatous areas. They quote extensively from the literature on related conditions. Although their patient did not show a significant alteration of the serum calcium values, they claim that such a deviation need not necessarily occur to prove their contention.

In this connection Longcope's (41) observations are of interest. He noted hypoglycemic crises in a sclerodermatous subject when breakfast was omitted for the purpose of a study of the basal metabolism. Careful study of the blood chemistry of this patient failed to reveal significant changes other than persistently low blood sugar values as compared to the accepted average readings of normal controls. Nevertheless, it is worthy of note that there is a very definite relationship between the blood sugar content on the one hand and the blood phosphorus value on the other. And in some at present unexplained manner there is a reciprocal relationship between the blood phosphorus and the serum calcium content. As Longcope points out, however ". . . . the disease affects the connective tissues of the entire body and the stroma of all organs may become involved in the pathologic process." He, therefore, advises caution in interpreting the findings in his series as necessarily indicative of an endocrine imbalance, since "the symptoms may have to be looked upon as secondary phenomena and not as indicative of any disturbances in the glands of internal secretion that could produce the disease." This aspect of the subject is worthy of further study.

Warthin (42) has recently drawn attention to the possible rôle of the reticulo-endothelial system in the causation of acrodynia (Swift's disease) and pellagra. In this connection Rowland's (43) concept of the possible implication of the reticulo-endothelial system as an etiological factor in the evolution of xanthoma should also be kept in mind. While it may at present seem far fetched to link up scleroderma, acrodynia, pellagra, xanthoma and other obscure skin manifestations, such a possibility cannot be dismissed lightly. Warthin (44), indeed, suggests that scleroderma may be a variant of the gouty state of altered metabolism; just as uric acid gout is characterized by a disturbance of uric acid metabolism, so may certain other states be the reflection of a disturbance of the lipoid metabolism abetted by a disability on the part of the re-

ticulo-endothelial system in its storage mechanism (lipoid gout), while other cases are characterized by a hyaline fibrosis (sclerotic gout). Wolf and Valette (40) make out an analogous case, except that they stress the altered calcium and phosphorus values of the organism. It is pertinent to note, also, that many of the reported cases showed a prompt and marked amelioration of their symptoms as the result of an altered dietetic regime. This possibility is at least worthy of further study.

### Case Report

Mrs. G. F., housewife, age 31, an Armenian, born in Greece and living in Michigan for many years, was admitted to the University Hospital Department of Internal Medicine, August 1, 1928, because of swelling of the hands and feet.

The *present illness* began some four months previous to admission with pain, swelling and a feeling of warmth in both knees and both ankles, more severe on the right. These symptoms persisted for one month. The swelling and redness subsided but the pain continued. One month before admission she complained also of pain, swelling and stiffness in the hands. Shortly before admission the swelling of the knees and ankles returned and at the time of admission there was swelling of the knees, ankles, and hands, with stiffness and pain on movement of these joints. During the course of the present illness there were vague gastro-intestinal symptoms consisting of anorexia, nausea, flatulence, vomiting and mild diarrhea. These symptoms were most marked about one month before admission. At this time she also suffered with general malaise, fever and chilliness, restlessness and insomnia. At times she had slight headaches. She lost about 10 pounds in the six months preceding admission.

*Past History*: She had measles as a child but no other exanthem. There had been no tuberculous contacts. Before tonsillectomy in April, 1927, she had been subject to frequent headaches but at only infrequent intervals since. Seven years before admission she was troubled at times with generalized pain in the legs, but of a mild character. At that time, also, she had vague digestive disturbances, characterized by "sour stomach and gas on the stomach." Occasionally nausea and generalized abdominal cramps were associated features. In April, 1927, her tonsils were removed. On July 29, 1927, she was admitted to the Gynecology Department, complaining of pain in the right side of the abdomen of about five years' duration, noticeable since the birth of her second child. At that time (July 1927) she also complained of ringing in the ears, especially the right. The diagnosis at that time was: Old lacerations of the pelvic floor and cervix uteri; visceroptosis; salpingitis of the Eustachian tubes. Surgical treatment was not advised.

There had been no history of venereal disease. She had had three pregnancies, the first of which terminated in miscarriage at seven months. She started to menstruate at 13, every 20 days, lasting 6 days, without pain. Her last menstrual period (previous to admission) was on July 22, 1928. There had at times been a profuse leucorrheal discharge necessitating the use of a napkin. Her husband has been in good health.

All her family were killed abroad during the war and she was unable to give further details as to their previous health. Physical examination revealed a fairly well nourished, slight female. The skin over the hands and feet was smooth, shiny, thickened and tense. The nails were not remarkable. The degree of pigmentation of the skin was compatible with her racial origin. The joints of the wrists, hands, ankles and feet were swollen and slightly tender. Passive movement of the fingers, toes, wrists and ankles was painful. There also was pain on active movement at the shoulders and elbows. There was some limitation of motion of the lower extremities due to pain. There was no perceptible muscle atrophy. The hair showed nothing significant. Except for a very slight enlargement of the cervical glands, the lymph nodes showed

nothing remarkable. There was slight suggestion of exophthalmos, but the thyroid was not palpably enlarged or adenomatous. The fundi were negative as also were the heart and lungs. The blood pressure was 115/65. Examination of the abdomen revealed slight tenderness in the right lower quadrant on deep palpation. Examination of the nervous system was entirely negative.

*Laboratory Examination*: *Urine*: Several specimens were negative. One specimen, 8-15-28, showed a trace of albumin with many white blood cells and rare granular and cellular casts. On 9-24-28, a catheterized specimen contained 20 red blood cells per high power field with some clumps of red blood cells. *Blood*: Hemoglobin 75 per cent on two occasions. Red blood cells about 4,000,000 on three occasions. White blood cells varied considerably. During her first three weeks in the hospital the white blood count was 8000 to 9000. During the next month it ranged from 12,000 to 24,000, the highest count being found during a complication of pneumonia. The final counts ranged around 10,000 to 12,000. The differential counts were not abnormal. The last routine blood study about twelve days befor death showed hemoglobin 55 per cent, red blood count 2,840,000 and white blood count 10,500. The Kahn test on the blood was negative. *Stools*: Three specimens were negative. *Sputum*: Four specimens were not remarkable. Agglutination tests for B. abortus, B. typhosus and B. paratyphosus A and B. were negative. Blood culture negative. Urine culture yielded only B. coli. B.M.R. 12-3-28, plus 56 per cent; 12-5-28, plus 20 per cent (tests reported as unsatisfactory). X-Rays—studies of right foot and right hand on August 3, 1928, showed no evidence of arthritis. Three X-ray examinations of the chest were reported as follows: 9-11-28—"Marked increase in the cardiac area. Very prominent enlargement of the left ventricle. Partial loss of the lung markings of the lower left side suggestive of a thin layer of fluid." 9-24-28—"Loss of lung markings in the lower left is more marked, suggestive of fluid or possibly consolidation. The cardiac shadow appears to have increased in size and we feel its contour would be suggestive of pericarditis." 10-9-28—"Marked increase in the cardiac area. Hypertrophy of the left ventricle, also the right auricle. Slight thickening of the interlobar pleura on the right side. Some increase in the hilum shadows, possibly due to their enlargement. Lung fields clear."

*Course in Hospital*: During the entire stay there was an irregular fever averaging 100° to 101° F. There was a persistent tachycardia averaging 100 to 120. Respiration rate was between 20 and 30. There was little change in symptoms for several weeks after entry except that slight cough with mucoid sputum developed. A careful search for foci of infection was made. Nothing was found other than caries of some of the teeth. One tooth was extracted on 8-8-28. About the first of September she began to complain of pain under the sternum particularly, and pain elsewhere in the chest difficult to localize. On September 10th, dullness, râles and bronchial breathing were heard over both bases. Several days later there was a suggestion of pericarditis by X-ray. The physical signs of pericarditis or effusion were absent. She was very ill at this time and recovery was doubtful. However, she gradually improved. All during this time she complained bitterly of joint pains previously mentioned and pain under the sternum. Treatment was entirely symptomatic, aimed particularly at relieving the joint symptoms. Her entire course in the hospital was steadily downward with variable periods of improvement and exacerbation. The skin gradually and steadily became firmer, less elastic and more deeply pigmented. Sweating decreased until it was almost absent. The skin was smooth, cold and shiny. These changes were most marked in the areas already mentioned, and in addition the skin over the whole body became involved to some degree. It became difficult, almost impossible, for the patient to move the extremities because of the stiffness of the skin. Finally, the face was so involved that she could open her mouth only a fraction of an inch. She grew gradually weaker and died 12-18-28.

*Necropsy* (December 19, 1928, at 11:45 P.M., twenty-eight hours after death). The

body was that of a poorly developed, thin, dolichomorphic adult female, 146 centimeters in length. There was marked emaciation. The head was symmetrical and showed no sign of trauma. The features were pinched and drawn. The pupils were in the intermediate position, the right slightly larger than the left. The irides were brown. The neck was medium in length. The thorax was long, narrow and flat. The abdomen was scaphoid. There were three small decubital ulcers over the sacrum, the largest being about 1 centimeter in diameter. There was also a small decubital ulcer over each acromial process. No anomalies of development were noted. Both legs and both arms were flexed at an angle of about 35° and could not be straightened out. The inability to straighten out the limbs was due to the tightness of the skin. There were no surgical wounds, scars or signs of trauma.

The skin was dark brown in color, the pigmentation uniformly distributed throughout. The skin was smooth, dry and shining. Over the bony prominences it was drawn tight like the head of a drum. It had entirely lost its elasticity and cut like hard leather. About the knees and elbows it was drawn down so tightly as to fix those limbs in a position of partial flexion. The skin broke and cracked with ease on attempted manipulation. The subcutaneous tissues shared in the firmness of the skin and appeared like scar tissue in texture. The hair was dark and abundant. The body hair was of normal female distribution. The teeth were in poor condition. The mucous membranes appeared normal. The muscles were markedly atrophic. Rigor mortis was present. The panniculus was extremely scant. There was no edema. Body heat was absent. There was hypostasis of dependent parts. There was nothing abnormal noted about the mouth, nose, ears, external genitalia or anus.

A section of cord was removed from the lower thoracic region. This showed no gross evidence of tract degeneration or other pathology. Permission for opening the head was not obtained.

The main incision revealed a scanty panniculus and atrophic, poorly developed muscles. The abdominal cavity contained 300 cubic centimeters of clear yellow fluid, no gas. The omentum hung free in the abdominal cavity. The liver edge was six centimeters below the ensiform, even with the rib margin in the right midclavicular line. The spleen was just above the rib margin. The bladder was contracted. The other abdominal organs were in normal anatomical relationship. The diaphragm was at the level of the fourth rib on the right; the fifth interspace on the left. The mammae were of the usual multiparous type. The costal cartilages cut with ease. The sternum showed no change in consistency. The left pleural cavity contained about 600 cubic centimeters of clear yellow fluid. There were a few light adhesions over the apex. The right pleural cavity contained about 400 cubic centimeters of clear yellow fluid. The lung margins were separated by about four centimeters in the anterior mediastinum. The cardiac apex was in the fifth interspace, almost in the anterior axillary line. The thymus could not be demonstrated grossly in the thymic fat. The pericardium was markedly distended and under pressure. The sac contained about 450 cubic centimeters of clear yellow fluid. The pericardium showed no thickening and there were no adhesions.

The heart measured 12 x 9 x 6 centimeters and weighed 280 grams. The heart was smaller than the cadaver's right fist and appeared reduced in size. The left ventricle, in rigor, made up the whole apex, and it was the left border of the pericardium rather than of the heart that reached to the anterior axillary line. The musculature of the left ventricle averaged 18 millimeters and showed a moderate brown atrophy. The cut surface showed many small irregular areas scattered through the musculature. These areas were orange-yellow in color and most marked under the epicardium, with strands extending inwards. They varied in size but were all quite small. No part of the musculature was free of these minute spots. The mitral orifice admitted two fingers and the flaps were slightly thickened. The aortic valve admitted the examiner's thumb; the cusps were negative. The musculature of

the right ventricle averaged about five millimeters, about two millimeters of which were fat. The musculature conformed in appearance to that of the left. The tricuspid valve admitted two fingers. The flaps appeared normal. The pulmonary valve admitted two fingers and also showed normal cusps. The coronary vessels were patent throughout and showed only slight evidence of sclerosis.

The left lung measured 21 x 18 x 7 centimeters and weighed 420 grams. There were a few adhesions at the apex. These were readily separated. The lung was air containing throughout. The surface was reddish-grey in color. Section showed some edema and congestion but no consolidation. There was no evidence of tuberculosis. The right lung measured 25 x 17 x 5 centimeters, and weighed 560 grams. There were no pleural adhesions. The upper two lobes were gray in color and of normal consistency but the lower lobe was reddish purple in color and felt firm. On section this part of the lung showed marked edema and congestion. The lobe was partly atelectatic but there were no definite areas of bronchopneumonia and pus could not be squeezed out of the bronchi. There was no gross evidence of tuberculosis. The bronchi appeared normal. There was moderate hyperplasia of the bronchial nodes. The pulmonary vessels were negative.

The aorta appeared normal in size and showed no gross signs of syphilis and only a slight degree of atherosclerosis. The thoracic portion of the esophagus was negative. The thoracic duct was not dissected. The thoracic vertebrae were negative.

The neck organs were removed at the level of the thyro-hyoid membrane. Larynx: The vocal cords were in the cadaveric position. The larynx showed neither ulceration nor neoplasm. There was a moderate degree of congestion of the tracheal mucosa which otherwise was negative. The cervical portion of the esophagus was negative.

The subcutaneous tissues about the thyroid gland showed a marked thickening and serous infiltration and appeared like edematous scar tissue. The thyroid was not enlarged and showed approximately normal colloid substance. The parathyroids showed no gross change.

The cervical lymph nodes were not enlarged. The cervical vessels and nerves appeared normal. The deep muscles of the neck were atrophic. The cervical vertebrae were negative.

The peritoneum was smooth and shining and there was no evidence of peritonitis. The spleen measured 14 x 9½ x 5 centimeters and weighed 230 grams. It showed some congestion and a moderate degree of lymphoid hyperplasia.

The intestines, large and small, were entirely negative grossly. The appendix measured 7 centimeters in length and was normal in position. It was free of adhesions and showed no evidence of previous inflammation. The duodenum was slightly bile stained. The bile passages were patent. The ampulla was about 8 centimeters distant from the pylorus. The stomach showed multiple petechiae but no ulceration. The mucosa had a smoothed out appearance.

The pancreas was normal in size and consistency and of normal appearance on section. The liver measured 25 x 17 x 11 centimeters and weighed 1440 grams. The capsule showed several old scarred areas. Two of these were at the lower border and caused a dimpling of the surface. The largest scar was on the diaphragmatic surface of the liver and extended into the substance of the organ. On section the organ showed congestion and a diffuse increase of stroma. The gall bladder showed no gross pathology. The portal vein was negative. The mesentery showed only a very small amount of fat. The mesenteric lymph nodes were somewhat hyperplastic.

The left adrenal was closely attached to the kidney but had a distinct capsule. On section the medulla showed far advanced autolysis, the cortex a moderate lipoidosis. The right adrenal was also closely attached to the adjacent kidney but with a distinct capsule intervening between the two organs. It conformed in all appearances to the left adrenal.

The left kidney measured 11 x 6 x 4 centimeters and weighed 150 grams. The cap-

sule stripped with ease, leaving a smooth surface. The surface showed many small dark brown specks. Between these were irregular areas of lighter brown pigmentation and irregular yellowish patches, giving to the organ a remarkable color effect. On section the cortex showed numerous fine, scattered areas similar to those noted in the cardiac musculature. These, however, were somewhat lighter in color and had the appearance of minute infarctions. The cortex was not reduced in thickness. The pyramids did not share in the areas of discoloration. The left ureter appeared normal. The right kidney measured 11 x 6 x 4 centimeters and weighed 160 grams. Its appearance was in every respect identical with that of the left side.

The abdominal aorta showed no gross evidence of spyhilis. The iliac vessels and ascending vena cava were negative. The lymph vessels in the abdominal cavity were not distended. The retroperitoneal lymph nodes appeared hyperplastic.

The submucosa of the rectum showed several areas of hemorrhage in the form of small, brown, raised spots. The mucosa was somewhat congested.

The bladder mucosa showed many rounded, elevated brown areas which felt firm and were free of ulcerations. They were scattered throughout the mucosa but most abundant at the trigone. The urethra was normal.

The vagina and vulvae were normal in appearance, the uterus normal in size and position. The tubes appeared normal and patent. There was a small cyst in the left ovary. The right ovary appeared normal.

Sections of skin were removed from various parts for microscopical examination.

The left knee joint was opened by a semilunar incision. The joint appeared pale. The cartilages showed no gross change. A piece of the synovial membrane and a section of the joint surface of the femur were removed for microscopic examination. At the time of autopsy the following gross pathological diagnoses were made:

Scleroderma. Extreme generalized arteriosclerosis with multiple minute infarcts of the heart muscle and kidneys. Cardiac failure with hydropericardium, bilateral hydrothorax and ascites. Atelectasis of the lower lobes of both lungs. Congestion and edema of the right lung (base). Petechial hemorrhages, recent and old, in the mucosa of the bladder and rectum. Atrophic arthritis of the left knee. Multiple decubital ulcers.

The *Microscopical Findings* were as follows: The *spinal cord* showed congestion and edema and early post mortem changes. There was no tract degeneration and there were no changes in the meninges. The *heart* showed marked subepicardial fatty infiltration with serous atrophy. There was atrophy of the heart muscle, with areas of increased stroma and fatty degenerative infiltration. The larger coronaries showed a well advanced sclerosis. There was sclerosis of the endocardium. The *aorta* showed a well advanced sclerosis without lipoidosis. There was no evidence of syphilis. The *lungs* showed marked congestion and edema and a chronic passive congestion with an acute exacerbation. There were numerous heart lesion cells. There were patches of early pneumonia and atelectasis. The *bronchial nodes* were heavily pigmented and markedly congested but free of tubercles. The *larynx* showed a chronic edema. *Thyroid* showed excessive colloid (colloid goiter) and increased stroma. There was no lymphoid hyperplasia. The fat stains showed a small amount of lipoidosis. *Spleen* showed chronic passive congestion, atrophy and relative increase of stroma. The *colon* showed chronic catarrh. *Appendix* showed old fibrosis and chronic catarrh. The *small intestine* showed atrophy and congestion. The *stomach* showed post mortem changes, marked atrophy and slight congestion. The *pancreas* showed slight atrophy and chronic passive congestion. The *liver* showed chronic passive congestion, atrophy, fatty infiltration and localized angioma cavernosum. The fat stains showed marked fatty infiltration. *Gall bladder* was negative. *Adrenals* showed a patchy lipoidosis but no infiltrations. *Peri-adrenal fat* showed serous atrophy and inflammatory infiltrations. *Kidneys* showed an acute progressive infarction of the outer portion of the cortex, with arteriosclerotic atrophy. There was

a chronic parenchymatous degenerative nephritis. The *lymph nodes* showed a chronic hyperplastic lymphadenitis. Chronic sinus catarrh. The *paravertebral ganglia* showed no changes. The diaphragm was negative. The *vertebrae* showed a moderately hyperplastic marrow. The *knee joint* was markedly atrophic, the bones osteoporotic and showing an absence of red marrow. The *skin* showed a very marked melanosis of the rete. There were numerous chromatophores in the corium. There was a diffuse sclerosis of the corium and subcutaneous tissues. There was atrophy of fat tissue and replacement by a dense, hyaline connective tissue. Scleroderma. *Striped muscles* were markedly atrophic, with interstitial fibrosis. The *urinary bladder* showed marked fibrosis of the submucosa. There were numerous cell nests of Brunn and a definite sclerosis of the submucosa. The *vagina* showed marked fibrosis of the wall. The *uterus* showed atrophy, the cervix dense fibrosis and a papillomatous hyperplasia of the squamous epithelium; also old grandular erosion. The *Fallopian tubes* showed old fibrosis. The *ovaries* showed marked fibrosis and atrophy; an unresolved corpus luteum in the left ovary.

*Final Pathological Diagnosis:* Scleroderma. Chronic atrophic arthritis, most marked in the knee and elbow joints. Advanced sclerosis of aorta and renal arterioles. Progressive infarction of the kidneys. Cardiac insufficiency. Hydropericardium, bilateral hydrothorax and ascites. Fatty liver. Lipoidosis of the kidneys. Early lobular pneumonia. Chronic hypertrophic cystitis with cells nests of Brunn and marked sclerosis of the submucosa. Chronic fibroid vaginitis. Cervical erosion. Large petechial hemorrhages in the bladder and rectum. Multiple decubital ulcers. Hemangioma cavernosum of the liver.

## Summary

The physical and autopsy findings of a case of scleroderma are reported. The local changes in the skin conform in all respects to those previously reported by other observers. They consist essentially of a fibrosis with hyalinization, with secondary atrophy of skin structures, with pigmentation. The striped muscles showed marked atrophy.

The patient presented moderate changes (fibrosis) in the thyroid and slight inflammatory and lipoid changes of the adrenals. These changes are so common without scleroderma that they can hardly be taken as evidence favoring the endocrinal origin of the condition.

The widespread fibrosis and sclerosis shown by this case in organs other than the skin might be interpreted as indicating some change in the general metabolism allied to gout. As writers have begun to characterize generalized xanthoma as evidence of a "lipoid gout" so *scleroderma* might be styled a "sclerotic" or "fibroid" gout in distinction to the ordinary "calcareous" or "urate" gout. Strength is given to the assumption by the fact that cases have been reported showing the coincident association of scleroderma and calcareous gout in the same individual. Numerous cases have been reported of scleroderma with calcareous concretions in the skin and subcutaneous tissues. There exists a whole series of affections of complex origin varying from trophic conditions of the skin associated with calcareous concretions to scleroderma. In the present case no lime-salt deposits were present, otherwise the hyalinization of the connective tissues is precisely the same as that seen in cases of scleroderma with nodular subcutaneous calcifications. Since the cases of scleroderma showing lime-salt concretions have been explained

on the basis of a phosphoremia under the influence of a functional disturbance of the endocrine system, those without calcification must apparently lack the calcifying factor of the dyscrasia. The process of lime-salt infiltration is a terminal stage, which appears only in certain cases, and in these only in certain zones. It is apparent that this whole series of conditions must be etiologically related, that they must represent the same metabolic and dysendocrinal background with a varying humoral factor, a lipoidemia in certain cases, in others a calcemia or phosphaturemia, in others a uricemia.

## REFERENCES


(1) Osler, Wm.: On diffuse scleroderma; with special reference to diagnosis and to the use of thyroid extract. Jour. Cutan. & Gen. Urinary Dis., XVI: 49 & 127, (Feb. & Mar.), 1898.

(2) Osler, Wm.: Modern Medicine, 1909. Lea & Febiger.

(3) Lewin & Heller: Die Sclerodermie, Berlin, 1895.

(4) Allbutt, T. C.: A System of Medicine, Vol. VIII, pp. 674-684, MacMillan & Co., New York, 1900.

(5) Hebra, quoted by Osler, reference 2.

(6) Oppenheim, quoted by Osler, reference 2.

(7) Watson, R.: Philosophical Transactions, Edin., 48: 175, 1754.

(8) Thirial, quoted by Crocker, H. R.: Clinical lectures on scleroderma, Lancet, 1: 191, (Jan. 31), 1895.

(9) Sequeira, J. H.: Diseases of the Skin, 3rd Ed., 1919.

(10) Stelwagon, H. W., Ibid., 9th Ed., 1921. Saunders & Co.

(11) MacLeod, J. M. H.: Ibid., 1920, Lewis & Co., London.

(12) Schamberg, J. F.: Ibid., 6th Ed., 1921.

(13) Castle, W. F.: The endocrine causation of scleroderma including morphoea, Brit. Jour. Derm. & Syph., 35: 255 & 303, (July-Aug.), 1923.

(14) Robinson, A. S.: Report of a case of scleroderma of the skin, Am. Jour. Med. Sc., 154: 657, (Nov.), 1917.

(15) Crocker, H. R.: Clinical Lectures on Scleroderma, Lancet, 1: 191, (Jan. 31), 1895.

(16) Herxheimer & Hartman: Ueber Acrodermatitis chronica atrophicans, Archiv., LXI: 57 & 255, 1902.

(17) Kingsbury, J.: A case of acrodermatitis chronica atrophicans with coexisting scleroderma, Jour. Cutan. Dis., 25: 414, (Sept.), 1907.

(18) Kanoky, J. P., and Sutton, R. L.: A comparative study of acrodermatitis chronica atrophicans and diffuse scleroderma with associated morphoea atrophica, Jour. Cutan. Dis. 27: 557, (Nov.), 1909.

(19) Cockayne, E. A.: Congenital and acquired scleroderma in childhood, Brit. Jour. Child. Dis., XIII: 225, (August), 1916.

(20) Jacquet: Ann. de Derm., 2 ser., 508, quoted by Castle, reference 13.

(21) Steven, J. C.: Glasgow Med. Jour., 26: 280, 1886, quoted by Stelwagon, reference 10.

(22) Josephovitch: Hemiscleroderma—abstr., Jour. Cutan. Dis., 34: 48, (June), 1916.

(23) Williams, C. M.: Case of diffuse scleroderma presenting unusual features, Arch. Derm. & Syph., 9: 187, (Feb. 24), 1924.

(24) Hektoen, L.: Diffuse scleroderma associated with chronic fibrous changes in the thyroid and great diminution in the amount of thyroidin; increase in the chromophile cells and of the colloid in the hypophysis. J. A. M. A. 28: 1240, (June 26), 1897.

(25) Uhlenhuth: Ueber diffuse Sclerodermie, Berlin. Klin. Wochenschr., 36: 207, (Mar. 6), 1899.

(26) Samouilson: Die la coexistence de la sclerodermie et des alterations des corps thyroide. These de Paris, July 21, 1899.

(27) Sequeira, J. H.: Four cases of sclerodermia associated with disease of the thyroid gland. Brit. Jour. Derm., 28: 31, (Jan.-Mar.), 1916.

(28) Graham Little, E. G.: Sclerodermia associated with Graves' Disease, and later myxoedema, benefiting conspicuously by implantation of human thyroid into the bone marrow, Proc. Royal Soc. Med., Dermatological Sect., Brit. Jour. Derm., 28: 124, (Ap.-June), 1916.

(29) Schultz: Jour. Cutan. Dis., 16: 49, 1898, quoted by Osler, reference 2.

(30) Winfield, J. M.: A case of scleroderma with symptoms simulating Addison's and Raynaud's disease: marked improvement from the administration of extract of suprarenal gland, Jour. Cutan. Dis., 22: 586, (Dec.), 1904.

(31) Jackson, G. T.: Two cases of scleroderma (case reports). Jour. Cutan. Dis., 27: 161, (April), 1909.

(32) Whitehouse, H. H.: Results of the Wassermann test in scleroderma, Journal Cutan. Dis., abstracted. J. A. M. A., 54: 412, (Jan. 29), 1910.

(33) Ayres, S.: Scleroderma as a possible manifestation of chronic arsenic poisoning, Arch. Derm. & Syph., 2: 747, (Dec.), 1920.

(34) Weller, C. V.: Personal communication to the author.

(35) Bramwell, B.: Diffuse sclerodermia; its frequency; its occurrence in stone masons; its treatment by fibrolysin; elevations of temperature due to fibrolysin injection. Edin. Med. Jour., 12: 387, (May), 1914.

(36) Sequeira, J.: Case report—Dermatological Society of London. Brit. Jour. Derm., 19: 242, (July), 1907.

(37) Roberts, L. R.: Scleroderma following injury in a child and resulting in contraction of the right index finger. Brit. Jour. Derm., 12: 1181, (April), 1900.

(38) Fox, W.: Proc. Roy. Soc. Med., Derm. Section, Feb. 1922, p. 14.

(39) Bancroft, J.: Scleroderma in relation to filaria sanguinis hominis, Lancet, 1: 380, (Feb. 28), 1898.

(40) Wolf, M., and Valette, A.: Relation of gout and scleroderma to calcium metabolism. Rev. de Méd., Paris, 43: 1121, 1926.

(41) Longcope, W. T.: Hypoglycemia in scleroderma: the metabolism in eight cases with reference to the function of the glands of internal secretion. J. A. M. A., 90: 1, (Jan. 6), 1928.

(42) Warthin, A. S.: So-called acrodynia or erythredema (Swift's disease): a pathologic study of two cases, Arch. Path. & Lab. Med., 1: 64, (Jan.), 1926.

(43) Rowland, R. S.: Xanthomatosis and the reticulo-endothelial system, Arch. Int. Med., 42: 611, (Nov.), 1928.

(44) Warthin, A. S.: Personal communication to the author.

# The Management of Some of the More Common Diseases of the Lower Bowel

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DISEASES of the anus and rectum are the most neglected of all the pathologic conditions affecting the human organism. Just why this is true is difficult to explain. Both women and men have an inherent reluctance in volunteering information concerning abnormal conditionst about the anus. They frequently use the various advertised nostrums to treat themselves, rather than seek medical advice. The medical profession has not considered seriously enough its responsibility in caring for the diseases of the lower bowel. Medical instructors casually mention anorectal diseases and medical journals are conspicuously short of articles bearing on this subject. Physicians often neglect to question their patients concerning symptoms which would lead to a proctoscopic examination. The busy physician will frequently prescribe an ointment or suppositories without making a rectal examination. Needless to say the results of such treatment are far from satisfactory.

The lower bowel is as accessible for examination as the nose and throat. Preliminary preparation by a simple enema is usually satisfactory. If a proctoscopic table is not available, the patient can be examined in the knee-shoulder position on an ordinary table. The instruments necessary are: a medium size sigmoidoscope and anoscope with direct light, finger cots, microscopic slides, and cotton swabs on long applicators. Where a water faucet is available, a long tube suction outfit can be used with advantage.

Indications for proctoscopy are: pain in or about the rectum or anus, bleeding from the anus, protrusions, pruritus, abnormal discharge, crawling sensation in the anus, and unexplained diarrhea or constipation. If every patient is questioned concerning these symptoms, it is surprising how many will acknowledge one or more being present. Examination of the anus should be made with the patient lying on the side with the knees flexed. In this position the sphincters are relaxed and very little pain is experienced. If the patient is allowed to strain as at stool, abnormal conditions such as fissures, and enlarged papillae, are brought into view. In the same manner also, internal hemorrhoids or polypi, are forced to protrude and can be seen. The examining finger should be inserted and by a rotary movement the anus and lower rectum carefully

palpated. After this examination the patient can be placed in the knee-shoulder position and proctoscopy performed.

Constipation is frequently the result of pathology in the lower bowel. Any condition which results in abnormal sphincteric contraction at the anus will eventually produce constipation or fecal impaction. Errors in habit, diet and sedentary living are productive of stasis in the colon. Hard dry fecal masses accumulating in the rectum produce an atony of the bowel wall and irritate the structures comprising the anus. Small fecaliths entering the crypts of Morgagni cause a chronic inflammation and subsequent abscess formation. Anal papillae become hypertrophied by irritation and the elongated papillae produce a contraction of the sphincters of the rectum. Engorgement of the hemorrhoidal plexus frequently results in hemorrhoids. When the anal mucosa is irritated and injured by hard feces, fissures are formed. The acrid discharge from infections involving the papillae, crypts and fissures, pours over the skin around the anus causing a pruritus Therefore patients with any of the above diseases may seek medical advice because of pruritus ani.

Diarrhea, unless profuse or frequent, is often ignored by the patient and physician. Intermittent loose stools may be due to errors in diet, achylia, chronic cholecystitis, protozoan infection, chronic colitis, proctitis or polyposis. Amebiasis is not uncommonly found in patients who have no diarrhea. Frequent watery stools accompanied by tenesmus is the most common cause of hemorrhoids. Stool examination should be made of every patient complaining of diarrhea.

Pruritus ani is fairly common and is a complication of some disease higher up in the bowel. Ointments and powders applied naturally give only temporary relief unless the cause is found and relieved. Every patient complaining of pruritus ani should have a careful examination of the anus and rectum.

Papillitis is hypertrophy of the anal papillae due to chronic irritation. These papillae may become enormously enlarged and protrude through the anus giving rise to a crawling sensation which is sometimes mistaken for worms.

Cryptitis usually accompanies papillitis. The crypts of Morgagni secrete the mucus which lubricates the feces in its passage through the anus. When they become infected, they expel an acrid fluid which is largely responsible for pruritus. When the infection in the crypts burrows through the mucosa, local abscesses form which may penetrate the perianal and perirectal spaces, producing large deep seated abscesses and subsequent fistulae. Cryptitis is a focus of infection which is frequently overlooked. There is an abundant blood supply to the anus and absorption of pus from this source can produce focal symptoms as easily as infected tonsils or septic teeth. One of our patients, a girl 22 years of age, had complained of progressive weakness, loss of weight and a daily rise of fever for four years. Frequent general examinations had been made by various physicians with negative findings. Her lungs were normal, her urine contained no pus and

her tonsils had been removed without relief. On careful questioning, she remembered on a few occasions to have noticed an itching and burning in the anus and a few times her underclothes were stained yellow. On anoscopic examination a large infected fissure and abscess of the post-anal crypts were found. There is no doubt of this being the focus which had previously been overlooked.

Fissure in ano with its sentinel pile, is a familiar picture to all. Text books tell us that ninety per cent are found in the posterior anal commissure. We have found almost as many anteriorly. Superficial fissures in the anal skin are often multiple. Deep fissures into the mucosa are usually single. Pain in the rectum during and after defecation is the outstanding symptom. If the fissure is deep enough to expose a nerve filament or sphincter muscle, the pain may be severe enough to require an opiate. Fresh bleeding after defecation always occurs when the fissure involves the anal mucosa. Patients with long standing fissures become anemic and the general health is impaired. Pruritus ani develops when the fissure becomes infected. The purulent discharge excoriates the skin around the anus producing a constant irritation which is impossible to control without correcting the fissure.

Peri-rectal abscesses are common. Infection from the crypts and fissures burrows through the mucosa above Hilton's white line and entering the peri-rectal spaces, finds a fertile field for abscess formation. The symptoms of a peri-rectal abscess are, pain in or around the rectum, extreme sensitiveness, fever, rigors and leucocytosis. Unless the abscess is drained early, it will penetrate the soft structures along the line of least resistance, pointing into the rectum, vagina or into the buttock on either side of the anal opening. If such an abscess is opened early much destruction of tissue is prevented. Fistulae usually result from these abscesses. Correction of fissures, cryptitis and constipation will greatly reduce the number of peri-rectal abscesses.

Fistula in ano is an infected tract through the soft structures of the buttocks or perineum, resulting from an incomplete healing of an old abscess. If the infection has burrowed in several directions the openings will be multiple. A blind fistula has only one opening. A complete fistula drains into a viscus and externally in the buttocks or perineum. Fistulous openings are quite characteristic. There is an eversion of the subcutaneous tissue, forming a teat-like elevation with an opening in the center from which a purulent material can be squeezed. Blind fistulae pointing into the rectum are often difficult to locate. One can often palpate the indurated area around the opening by the examining finger. A direct view through the anoscope reveals the sinus and makes the diagnosis certain. The vast majority of fistulae are not tuberculous though fistulous tracts are frequent in patients with pulmonary tuberculosis.

Hemorrhoids, both internal and external, are the result of mechanical pressure upon or irritation of the hemorrhoidal plexus. The mechanical pressure by the pregnant uterus and the straining during childbirth frequently

result in large internal hemorrhoids. Constipation, fecal impaction, and diarrhea from disease or purgation cause a chronic congestion of the veins of the lower rectum and subsequent varicosity. Internal hemorrhoids are covered with mucus membrane and originate above the internal sphincter. They may protrude en masse forming the well known grape-like cluster and become very painful. This variety frequently bleeds profusely and if untreated will cause a partial prolapse of the rectum. When contraction of the internal sphincter cuts off the return circulation, strangulation occurs. This condition is very painful and demands emergency treatment. External hemorrhoids are covered by skin, having their origin below Hilton's white line. A large external hemorrhoid may become thrombosed causing acute pain and swelling.

In making the examination for hemorrhoids, the patient should be placed on his side with the knees flexed on the abdomen. The buttocks are separated and he is asked to strain as at stool. The hemorrhoids will present at the anal opening. The gloved index finger well lubricated is gently inserted and careful palpation with a circular movement made to determine the extent of the hemorrhoids. Later, the patient can be examined through the anoscope in the knee-shoulder position.

Polypus. Polypi may be found singly or in large groups and will be found complicating other rectal diseases. The usual location of a single tumor is in the lower rectum about two inches from the anus. It sometimes grows on a long pedicle and may protrude outside the anal opening. Multiple polypi may fill the entire colon and cause few symptoms. The usual symptoms are: abnormal protrusion, bleeding, diarrhea, and partial obstruction. Polypi are usually benign though they may undergo malignant degeneration. They are more often found in young people.

Strictures of the rectum are the result of previous inflammation. All of the cases have their origin in some previous intra-rectal injury, or irritation due to dysentery, carcinoma, syphilis, tuberculosis or muscular spasm. The symptoms are those of obstruction due to the narrowing of the anal canal. The stools will be soft, small, thin and contain mucus and sometimes blood. Gaseous distension from incomplete evacuation, vague pains in the pelvis or back and general malaise from autointoxication. Syphilitic strictures are far more common in women than in men.

Malignancy. Cancer occurs in the rectum more commonly than in any other part of the colon. The favorite sites are the lower dilated portion or ampulla and the rectosigmoid. Ulceration occurs early. The onset is insidious with no loss of weight or cachexia in the beginning but rapid loss in the late stage. There is often a sensation of weight and pressure in the rectum accompanied by alternate diarrhea and constipation. The stools are blood stained when ulceration has occurred. Where the cancer is located in the ampulla, it can be palpated by the examining finger. In the rectosigmoid it can be seen through the proctoscope. Malignancy of the rectum is more common in men than in

women. A characteristic feature about it is that it often occurs in individuals under thirty years of age. Metastasis occurs by way of the lymphatics and veins. The diagnosis is made by the symptoms, the examining finger when in the ampulla, the proctoscope when higher up in the rectum and by the deformity seen in an opaque enema. Patients in the cancer age who complain of sudden onset of constipation or alternate constipation and diarrhea, who have symptoms of partial obstruction and blood stained stools, should be carefully examined for rectal carcinoma. In the end stage when loss of weight and cachexia appear, the condition is usually hopeless because of metastasis having already occurred.

Management of the diseases of the anus and rectum. Treatment may be divided into three classes:

1. Prophylactic.
2. Medical.
3. Surgical combined with medical.

Prophylactic treatment consists of hygienic measures, cleanliness, correction of constipation, diarrhea, the proper mastication of food, the drinking of an abundance of water, and the avoidance of using unclean nozzles on enema syringes.

Medical management is beneficial in simple inflammatory conditions such as cryptitis, papillitis, superficial fissure and mild hemorrhoids. We have seen some excellent results from the application of 5% mercurochrome (220 soluble) on cotton swabs, followed by the instillation of two ounces of extract of witch hazel into the rectum. Treatments are given every day at first, then every other day. As the condition improves, treatments are given twice weekly until the lesion has healed. The instillation of four ounces of olive oil at night or suppositories containing a mild antiseptic such as boric acid, zinc oxid and ichthyol is often a helpful adjunct to the local treatments.

Surgical treatment is necessary in all cases of deep seated cryptitis, elongated papillae, deep fissures, prolapsing, strangulated, thrombosed or bleeding hemorrhoids, polypi, abscesses, fistulae and malignancies.

It is our custom to follow up all our surgical cases with medical treatment until the wounds have healed. Convalescence is shortened, the wounds heal more kindly, the patient is more comfortable and the end results are far more satisfactory when this procedure is followed. Beginning on the fourth day, when the bowels have moved, we take the patient to the treatment room daily for treatment similar to that outlined under medical management. The wounds are cleansed and the dressing changed after each bowel movement and in the case of postoperative fistulae, the iodoform gauze packs are changed daily. This requires a great deal of work but the results more than justify the effort expended.

In conclusion I wish to emphasize the importance of a careful examination of the lower bowel, in all patients who present symptoms pointing to disease in this region. Treatment should continue until healing has occurred. In disease of long standing many weeks may be required to restore the bowel to normal function. Patients as a rule co-operate well and are grateful for the relief obtained.

# Glycosuria and Diabetes

By A. Galambos, M.D., *New York City*

At the February meeting of the Progressive Medical Society of New York Dr. Louis I. Harris, Health Commissioner of New York City, called our attention to the significance of the Periodic Health Examinations, emphasizing the importance of age. The usefulness of the periodic health examination can hardly be demonstrated in a more impressive way than in the practical case of glycosuria and diabetes. In this special instance the periodic health examination undoubtedly increases the number of the early diagnosed cases and consequently if there is any value in the early diagnosis, this swings the ratio between the mild and severe, respectively between the early and neglected cases in favor of the frequency of the mild and earlier forms of the disease.

Consensus of opinion, both public and professional, is prone to consider glycosuria and diabetes as synonyms, and as a practical demonstration the life insurance companies find any slight degree of glycosuria, without further analysis of the case, sufficient ground for refusal to issue policies.

Still we safely can say, that both conditions are not identical: presence of dextrose in the urine does not necessarily mean diabetes, just as albuminuria is not identical with nephritis. There are principal differences between both. While glycosuria is only a symptom—certainly the most important and characteristic for diabetes—which can as a concomitant symptom be encountered in various other morbid conditions too, diabetes is a disease-entity, characterized by a faulty metabolism—not solely, but principally—of the carbohydrates. While most of the glycosurias are innocent, often transitional occurrences, without progressive tendency, diabetes is, even in its mildest form, a persistent disease, which may progress and may, due to its inter-relation with the other organs, affect the entire system.

Contrary to the varying etiology of the various forms of glycosurias, the uniformity of that of diabetes mellitus cases is significant. Diabetes mellitus is actually a true disease-entity. Still, on closer view we may discriminate between the type of diabetes of the young and of older people. This differentiation is more than something attributable to the different ages.

The diabetes of corpulent, overnourished, elderly people offers a more favorable prognosis than the diabetes of lean children and young adults. But the prognosis is not better because they are stout or overfed. Indeed they develop diabetes because they carry on this mode of living and their over-

indulgence in nourishment predisposes to its development. Moreover, the diabetes of older people is often due to degenerative processes in the vessels, not different in character from those met with in other organs. Diabetes from these causes has an easily determined etiology and accordingly it can easily be combated or improved. It is not always a disease sui generis; it is often a condition dependent on overfeeding, like obesity. Surplus of energy in the first instance is shown as sugar in the urine, in the other it leads to an excess of fat. This diabetes is strikingly different from diabetes juvenilis.

Diabetes juvenilis represents a very severe, and before the insulin era an absolutely deadly disease. These young people need energy not only for keeping their equilibrium, they need surplus of energy for their growth as well. But unfortunately these severe diabetics (and that is the reason they are severe) cannot utilize carbohydrates, and this metabolic disturbance, as is well known, secondarily affects the fat metabolism as well. Both impairments combined—since no energy can be furnished to keep up life—make living impossible. They inevitably lose weight since they cannot utilize the calories in their diet. That makes them severely sick, therefore they become more lean. If they could be kept in equilibrium, or if they could gain weight, their life would not be seriously endangered; this would be equivalent to utilization of calories. Fattening is an evidence of cure here—not the aim, but rather a natural effect of improved condition—like weight-reduction in the diabetes of the obese and of elderly individuals. Of course stout or overfed persons also may develop true, severe diabetes, just as the diabetes of meager persons can also be mild.

In diabetes juvenilis the diabetes is primary; general weakness and undernutrition are secondary. In diabetes of older individuals, corpulence is primary and diabetes develops consecutively. The importance of obesity as primary factor, in these cases, is also emphasized by Joslin, Mosenthal, etc.

The diabetic, just like a normal man, should have his normal, average weight; the spare should be fattened, the stout should be reduced, not only because an average weight is optimal, but for the sake of combating the ill health which is etiologically important in mild cases of those in later life, or to correct emaciation due to the severity of the disease in diabetes juvenilis.

Weight apposition offers a better prognosis in young people, while reduction in weight should always be aimed at in obese adults. If the constitutional condition seems to have a causative relationship to the development of the disease, the opposite state should always be aimed at.

But even if there is a discrimination in the clinical appearance, prognosis, etc., between both forms, the faulty metabolic disturbance is in all these cases identical, only quantitatively different.

Diabetes mellitus is characterized by a faulty mechanism not only of the carbohydrate, but also of the fat and protein metabolism. The anomaly of the carbohydrate metabolism should

not be dwelt upon. It is too well known. None the less important are the fatty metabolic disturbances, which are, as a rule, encountered only in the more severe cases. It is not important from this point of view, whether or not this is the case because the fat burns only in the flame of the carbohydrates, as stated by Rosenfeld and as recently experimentally proven by Shaffer, and accordingly as long as the carbohydrates are properly utilized, no change in the fatty metabolism occurs, or perhaps because a partial or incipient change in the pancreas affects only the carbohydrate metabolism, and farther advanced alterations can bring on changes in the katabolism of the fats only. The fact is, that the danger connected with diabetes was and still is, more to be seen in the metabolic disturbance of the fat, than in that of the carbohydrates. Acetone, diabetic acid and beta-oxy-butyric acid, the scourge to diabetes, are representing the intermediary products of the fatty metabolism, indicating that the fatty acids cannot be oxidized to their end-products.

Not all the fats, only those with even number of C atom endanger the system with the formation of the beta-oxy-butyric acid; Max Kahn's intarvin, a synthetic fat with odd number of C atom should even by a severe diabetic be broken down to its end-products to $H_2O + CO_2$, without forming aceton-bodies. Louis C. Johnson calls incomplete oxidation of the fatty acids: ketosis, and if these substances accumulate faster than they can be excreted, we have acidosis or diminished bicarbonate of the blood. The degree of acidosis can be measured either directly by the determination of the actual amount of the aceton-bodies or indirectly by estimating the amount of the alkaline reserve of the blood plasma, by determining its $CO_2$ combining power.

In case of insufficient glucose-oxidation the decomposition of the fats is incomplete. It is assumed that the oxidation of one molecule glucose suffices to completely oxidize 1 molecule fatty acid. Furthermore incomplete breaking down of 1 molecule fatty acid will produce one molecule ketone body. According to P. A. Shaffer and Wilder, if the molecule of fat to be burned is two or more times larger than the molecules of the actually burned carbohydrates (from this standpoint it is unimportant whether the carbohydrates are not ingested as in starvation, or not utilized as in diabetes), the katabolism of the fat stops at the intermediary stage of the aceton-bodies. According to Woodyatt, a safe ketogenetic anti-ketogenetic ratio, i.e. FA/G is 1.5 or less, in other words $\frac{0.46\ P+0.90\ F}{C+0.58\ P+0.10\ F}$ should be 1.5 or less, being the source of F, C, P, exogenous or endogenous, or F should not exceed $2\ C+\frac{P}{2}$ especially with diets of magnitudes above the basal caloric requirement, because the surplus of calories will—at the same body weight—increase the acidosis concentration, i.e. $\frac{(\text{aceton bodies})}{\text{kg}}$ ratio.

The lipoid changes in the blood

serum, and the increase of its cholesterol content as manifestations of the fatty metabolic disturbances should only be mentioned here.

The knowledge of the metabolic disturbances of the proteins in diabetes mellitus is generally less known. Since, during the decomposition of the proteins in severest experimental phlorizin diabetes we find the amount of dextrose 3.65 times higher than that of the nitrogen (1 gm. of N. being derived from 6.25 gms. of protein) as expressed by the D/N ratio, it can be easily calculated that the dextrose production from protein amounts to its 58% by weight. In other words the proteins during their metabolism split off 58% amino-acids, convertible into glucose, with antiketogenetic effect.

Since a long time it has been known to the clinicians that some of the diabetics, the so-called protein-sensitive diabetics, do not tolerate the proteins very well, i.e. these diabetics respond to the increase of the protein in the diet with the prompt rise of glycosuria. Each case behaved somewhat differently, and each case separately had to be tried out for its protein-sensitiveness.

Outside of this, there is also another type of metabolic disturbance of the proteins, which is more analogous to, but independent from those of the carbohydrates and fats. I found fifteen years ago, with my co-worker Dr. B. Tausz, that the urine in most of the cases of severe diabetes mellitus contained increased amount of amino-acids.

Amino-acids are as well known hydrolytic products of the proteins through the intermediary stage of meta-proteins, proteoses, peptones, polypeptids. But as according to Lengyel and Hary, during the ferment-reactions of the decomposed proteins in the stomach, no heat-production will be observed, hyperaminosuria means from energetical view-point total loss of the respective proteins.

The hyperaminosuria found in our cases was an absolute, a relative and an alimentary one, pointing to the insufficient utilization of the proteins. Hyperaminosuria had after all kindred significance and was analogous to the acidosis due to the insufficiency of the fatty metabolic changes.

We soon completed our work by the complementary experimental part, and found hyperaminosuria in pancreas-diabetes of dogs, i.e., after preliminary pancreas extirpation had been performed. The hyperaminosuria is caused only by the loss of the internal secretion of the pancreas, because ligature of both of the pancreatic ducts had no effect upon the degree of the excretion of the amino-acids.

The findings of the diabetic hyperaminosuria were soon corroborated by a number of authors (among them: M. Labbe and H. Bith; H. Labbe; Pribram and J. Loewy; W. Loeffler, etc.).

Accordingly the protein metabolism suffers, partly because its decomposition may stop at the stage of amino-acids, and partly because another large amount of amino-acids enhances through its antiketogenetic effect the sugar-excretion, acting similarly to dextrose.

The glycosurias have a varying eti-

ology and pathology, and accordingly their interpretation and significance cannot be uniform. The best studied form of the non-diabetic glycosurias is the clinically known renal diabetes, and the phlorizin glycosuria, which is often considered the experimental form of the renal diabetes.

Outside of these forms there are other types of the non-diabetic glycosurias, as those after shock, trauma, cerebral hemorrhage, commotion of the brain, injury, experimental piqure, in asphyxia, narcosis, infectious and post-infectious conditions, arterial hypertension, chronic nephritic conditions, imbalance of the internal secretory organs, as the primary and compensatory hyperfunction of the thyroid, adrenals, hypophysis, or administration of their active principles as that of the adrenalin, hypophysis extract, thyroxin, etc., to give only an idea as to the multitude and heterogenicity of these forms.

If we want to make a differentiation between glycosurias of any origin and diabetes mellitus, of any severity, the following questions should be cleared up:

(1) Presence or absence of reducing substance in urine;

(2) In case of its presence, identification of its dextrose nature;

(3) Functional urine test with 50 or 100 gms. of dextrose.

(4) Blood-sugar determination on fasting.

(5) Sugar tolerance curve, i.e., blood-sugar estimation before, and 1-2-4 -hours after the ingestion of 50 or 100 gms. dextrose (last 2 requirements only if feasible).

As an explanation to the 3rd requirement: The urine should be collected and examined 2 hours after the ingestion of about 100 gms. of sugar or somewhat more other carbohydrates, taken in a convenient way, in form of a breakfast, as a functional test meal.

If this functional test is done in cases of diabetes mellitus, the amount of the dextrose in the urine increases considerably. If any other form of glycosuria is present, with the chief representative of the renal type of glycosurias, the small amount of glycosuria which was present in the urine on fasting, or at any time during the examination, will, as a rule, stay as it was or even as the case very often is, decrease or disappear.

In my judgment this is the most simple, practical and rational test for differentiation.

As an explanation to the 5th requirement, when instead of the blood-sugar curve, only one determination can be taken, the most important examination is the one taken 2 hours after the ingestion of glucose. The blood-sugar value after the ingestion of glucose returns within 2 hours to normal figures, respectively to the figures found before the test meal was taken. This is the case under physiological and also under most of the pathological conditions. We count in this latter group also the various glycosurias. In true diabetes mellitus not only the height of the blood-sugar level is raised compared with those under normal conditions, but, and this seems to be the most characteristic feature, the return to normalcy never occurs

within 2 hours; the delay may take a much longer period of time due to, and in accordance, with the severity, of the individual case. But, like glycosuria, also hyperglycemia, or even a positive sugar tolerance test alone cannot be considered as absolutely proving the existence of a true diabetes mellitus, as emphasized also by Mosenthal.

There are different aberrations, referring to or characterizing certain parts of this mechanism. Hugh McLean calls "lag" cases, in which the blood-sugar level surpassing the physiological threshold value returns within 2 hours to normalcy. The elevation of the blood-sugar level above the physiological threshold value brings on glycosuria, which, however, disappears within 2 hours after the ingestion of the carbohydrates.

Aside from the lowered renal threshold value, its increase also deserves our attention. The increased renal threshold value is encountered in the far advanced cases of chronic diabetes mellitus, and also in those combined with chronic nephritic conditions. Sometimes there is no such basic disease to be found and if the increase of the threshold goes beyond certain limits, the glycosuria may be entirely missed in the simultaneous presence of hyperglycemia. Polyuria and polydipsia may mask the diabetes mellitus and mislead to the erroneous diagnosis of diabetes insipidus, as long as the hyperglycemia does not clear up the nature of the situation, namely, the inhibitory function of the sugar-excretion, in other words: diabetes mellitus with increased renal threshold value for glucose, as in one case observed by R. Balint.

J. Andresen and A. Schmidt describe high degrees of hyperglycemia without glycosuria in different infectious diseases, so e.g. in typhoid fever, dysentery and especially in scarlet fever, where they found blood-sugar values around 0.3% (without glycosuria) in contrast to measles, in which disease normal glycemia seems to be characteristic.

It is well to remember and this cannot be emphasized enough, as we find it accentuated in v. Noorden's works, that the mild and especially the incipient cases of diabetes mellitus may vary to a great extent, and that there are diabetes mellitus cases in their earliest stage similar to those diagnosed as diabetes renalis.

Not only the different forms of glycosurias are etiologically and pathologically different, but its chief representative, the diabetes renalis, is, even today, according to different authors, interpreted in entirely different ways.

In my opinion, diabetes renalis is principally different from diabetes mellitus, notwithstanding the fact that the differentiation can—especially in the earliest manifestation of the disease—be sometimes difficult or not even possible. As a rule, in diabetes mellitus, the diabetes is persistent even if the glycosuria is not (as in the mild cases); while in renal diabetes the glycosuria is persistent even if the diabetes, i.e., the disease is not (as in the transitional cases).

In renal diabetes, we expect a persistent glycosuria, i.e., any portion of the urine contains dextrose, regardless

of food taking; the glycosuria is with very few exceptions, mild, the dextrose concentration varying between 0.1-0.5%. The persistency of glycosuria is very characteristic, and this should be emphasized as against the mild cases of diabetes mellitus, in which latter case aglycosuria always can easily and within a day or so be achieved. In renal diabetes the small amount of dextrose, often only traces, will no matter how strict carbohydrate-free diet is given, persist. Lewis and Mosenthal observed only after a six days' lasting starvation, disappearance of the glycosuria. A slight degree of stubbornly persistent glycosuria, independent of food-taking, is the most significant feature of the diabetes renalis.

The diagnosis of renal diabetes is never complete without blood-sugar determination. The blood-sugar is always low; normal, low-normal or subnormal; this is the case, not only on fasting, but also after administering a great amount of carbohydrates. The physiological renal threshold value for glucose is never surpassed, and still there is a continuous glycosuria. The glycosuria is always independent of the height of the blood-sugar level. There is no response between carbohydrate intake and the degree of glycosuria, but if there is any, as it sometimes may occur, we find the interesting reverse type; on increasing the carbohydrates in food the degree of glycosuria may lower. Gibson and Larimer found that in renal diabetes the injection of 50 gms. of glucose lowered the glycemia to such an extent that hypoglycemic reaction may appear.

Although most cases of renal diabetes are mild, there does not exist any principal reason why occasionally a higher degree of glycosuria could not be met with. And actually, there are a few cases published in the literature with considerable severity. Out of the 3 cases of renal diabetes published by me within the last 15 years, the first one referred to a very severe case with a high degree of acidosis.

In this latter case I was able to show, that although the case otherwise proved to be a classical form of renal diabetes, its severity differed in no way from very severe cases of diabetes mellitus. The daily loss through dextrose excretion amounted to values around 150-200 gms., and the degree of acidosis was also remarkable. In this case, the first in the literature, R. Q. determinations were performed and it was found that the same was very low, 0.709, just as in cases of severe diabetes mellitus, and it did not even after the ingestion of 150 gms. of dextrose show any increase.

Contrary to the continuity of the glycosuria in renal diabetes, the sugar excretion in mild diabetes mellitus is intermittent. In these cases the elimination of the dextrose is not a continuous process, it greatly depends on the carbohydrate content of the food ingested within the last few hours. In the mildest cases of diabetes mellitus when the twenty-four hour urine is free of sugar, the sample voided 2 hours or still more so 45-75 minutes after the carbohydrate containing meals, may contain dextrose in suffi-

cient concentration for its recognition. Therefore, in cases of mildest or questionable diabetes mellitus the two hour sample should be examined. This is the test for the detection of the post-cenal temporary glycosuria.

This question brings up the problem of the carbohydrate tolerance, which used to be stated for twenty-four hours. Instead of this, I have recommended expressing at the same time the tolerance for the single meals too, because if the patient can utilize for instance 75 gms. of carbohydrates taken at one meal, he can tolerate 150 gms. of carbohydrates when he takes one-half of this amount twice daily, 225 gms., when he takes one-third the amount three times daily.

The knowledge of the post-cenal temporary glycosuria is important also from the standpoint of the maintenance diet. On the preliminary test diet we are slowly, progressively increasing the daily amount of dextrose, on an otherwise isocaloric diet until the first dextrose appears in the urine. This is expressed: as the tolerance for sugar. More important, because more sensitive than this test is the examination for dextrose utilization. This limit is reached the moment the dextrose ingested cannot be utilized totally, and it starts, before glycosuria sets in, to raise the dextrose level in the blood. Rise of the blood-sugar level within the renal threshold value is as I found practically coincident in time with the temporary post-cenal glycosuria, i.e., when the 24-hour urine is free of sugar, but the sample voided 2 hours or especially 45-75 minutes after the meal, contains some dextrose. This is the period between the utilization and tolerance. In other words, if we want to put the patient on a maintenance diet (the carbohydrates being divided equally into 3 parts) the maintenance diet should precede the diet upon which the first post-cenal temporary glycosuria was observed.

The striking respiratory findings in renal diabetes opened the field to further study in which I was able to show with my co-worker, Dr. E. Schill, that in the experimental phloridzin diabetes in dogs, the R. Q. was equally low, and that severely phloridzined dogs lost the ability to oxidize dextrose. The severity of the phloridzinisation marked the degree of this inhibitory function. Deprivation of the system from dextrose through glycosuria could not be made responsible for the failing rise in R. Q., because even if superfluous doses of sugar were ingested or injected, and even if double-sided nephrectomy was performed, which stopped the glycosuria at once, the inability to burn sugar, was uniformly present in our cases.

This important fact, namely the lost power of combustion of dextrose in phloridzin poisoning, is able to throw quite a new light on the pathogenesis of the different glycosurias. This holds true, even if met with the disfavor of an author like von Noorden, who, although he could not present any positive arguments against it, yet in his criticism disclosed nothing but aversion to some new facts which might have compelled him to formulate ideas for the explanation of the glycosurias in a different way from that which he had done previously. He

found our results so striking, however, that he felt impelled to write in his book as follows:

"Nun hat mit den gleichen Methoden, mittels derer man jene Theorie stuetzt, den Stoffwechsel beim akuten Phloridzindiabetes untersucht (A. Galambos und E. Schill). Man kam zum gleichen Resultat: scheinbar findet kein Verbrauch von Zucker im maximalen Phloridzindiabetes statt. Das hätte doch ein Warnungssignal sein sollen, man hätte sich sagen sollen, dass eben die Methode (Messung des respiratorischen Quotienten nach Kohlenhydratzufuhr, Kap. IV), nicht das beweist, was man von ihr erwartet. Aber die Authoren haben sich nicht einmal die Mühe gegeben, sich mit den Einwänden auseinanderzusetzen, die ich schon vor Jahren gegen diese Methode erhob. Wie in aller Welt wollen sie erklären dass durch die Phloridzinvergiftung auf einmal, fast von einer Stunde zur anderem, ein Grundgesetz der Biologie, der Zuckerverbrauch, in den Geweben unterbrochen werden und nach wenigen Stunden, wenn das Phloridzin ausgeschieden ist, wieder voll in Kraft treten soll? Wäre es nicht richtiger gewesen, angesichts solcher ungeheuerlichen Folgerung an der Beweiskraft der Methode zu zweifeln und auch ihre Beweiskraft fuer die Zustande im Diabetes in Frage zu ziehen?"

Noorden's objections to this new fact seem to be nullified by the work of Lusk and Nash and Benedict who are unanimous in corroborating the fact first discovered by us.

Ringer found that 75 gms. of glucose given to a phloridzinized dog is completely eliminated in the urine. Lusk stated that the ingestion of this large quantity of sugar in no way affects the respiratory quotient. He writes: "It is therefore evident that the completely phloridzinized dog has lost the power of oxidizing glucose." Stanley Benedict administered glucose to phloridzinized dogs in an amount sufficient to cause the blood-sugar to rise above the normal, but a rise of R. Q. did not occur, showing that sugar is present in ample concentration though it remains chemically untouched.

M. Ringer says: "A completely phloridzinized animal suffers from two essential incapacities. One is the inability to utilize sugar, from which defect follows the familiar train of pathological findings that constitute the picture of true diabetes. This is well established. The other defect relates to the inability of the kidneys to resorb the sugar (they filter from the blood), resulting in a persistent glycosuria and the hypoglycemia, which distinguishes phloridzin diabetes from pancreatic diabetes. This much lowered renal threshold for sugar has somewhat confused the essential diabetic character of the phloridzin injury. Indeed it is held in many quarters that the failure of the phloridzinized body to metabolize glucose is due to the subnormal blood-sugar induced by the kidney leak. One cannot drink water from a sieve. Recently, Nash and Benedict have put the quietus on this view by giving glucose in sufficient amounts to induce protracted hyperglycemia in phloridzinized dogs and recovered it quantitatively in the urine.

That phloridzin produces a real lesion of the sugar-burning mechanism, can no longer be held problematic"

Unfortunately, it escaped the attention of Lusk, Benedict, Ringer, etc., that this new fact of the impairment of the oxidizability for dextrose in phloridzin glycosuria was discovered by A. Galambos and E. Schill, who published their experiments in this line in the Zeitschrift fuer experimentelle Pathologie and Therapie in 1914. But this is a question of priority only and as such is of secondary importance, and does not touch the main point—the fact as detailed above. Lusk, Nash, and Benedict, also their predecessors, the pioneers, Reilly, Nolan and Lusk, Loewy, Stiles and Lusk, Rosenfeld, etc., gave dextrose per os or subcutaneously to the phloridzined animal and found quantitatively in the urine the amount of glucose ingested; from this they concluded that this same amount of sugar must have escaped combustion in the tissues. Galambos and Schill are the only investigators who used the method of the respiratory metabolism. By both methods the same conclusions were reached.

The combustibility of dextrose which was considered impaired in severe diabetes, and present in renal or phloridzin glycosuria can after all not serve as a differentiation sign; they uniformly fail in all these conditions, provided the condition has been developed far enough.

After all, renal diabetes can easily and with sufficient accuracy be differentiated from diabetes mellitus. The most characteristic features of these three conditions, grouped respectively according to their resemblances and differences to each other, are summed up in the following table:

| | *Diabetes Mellitus* | *Phloridzin Diabetes* | *Renal Diabetes* |
|---|---|---|---|
| Glycosuria. | Present | Present | Present |
| Glycemia. | Increased | Lowered or normal | Lowered or normal |
| Dextrose threshold of kidneys. | Normal: Later increased | Lowered | Lowered |
| Glycosuria after CH intake. | Rises | Rises | |
| Glycosuria after protein intake. | May rise | May rise | |
| Glycosuria after the same diet. | Unchanged | Unchanged | Varying |
| Glycosuria after CH reduction. | May disappear | Present | Present, may rise |
| Parallelism between blood-sugar and urine sugar concentration. | Present more or less | Mostly present | Absent |
| R. Q. in severe cases. | Low | Low | Low |
| Effect of CH intake on R. Q. in severe cases. | Missing | Missing | Missing |
| Acidosis in severe cases. | Present | Present | Present |
| Dyszooamylia (lack of storage). | Present | Present | Missing |
| Response in glycosuria after insulin. | Present | Present | Missing |
| Curative effect of both diet and insulin. | Present | | Absent |

Though there is a great resemblance between these 3 conditions, differentiation is nevertheless important, especially from the view point of the prognosis and therapy.

The prognosis of diabetes renalis is in most of the cases good; in severe cases it is less favorable, not only on account of the loss of dextrose through glycosuria, and a possible acidosis, but also because no dietary regulation is effectual, and insulin is of no avail. Fortunately severe cases are very rare.

As for the therapy: no dietary regulation is required; insulin is not only inefficient, it is in fact, on account of its blood-sugar reducing effect, dangerous. The low blood-sugar level may easily drop to values causing hypoglycemic reactions. Ineffectiveness of insulin is important not only from the therapeutic, but also from the diagnostic view point.

In diabetes mellitus the therapy consists of administration of a proper diet and insulin.

The diet is calorimetrically computed. The basal caloric requirement is determined either on ground of the weight or of the surface area computed with the aid of Du Bois' chart. After deducting the basal protein requirement (P.) which is 2/3 gm. per kilogram weight, the balance is supplied by fats and carbohydrates. On computing the amount of the carbohydrates, there are to be considered the carbohydrate tolerance of the patient, the safety relative to the ketogenetic-antiketogenetic ratio and the total caloric requirement. Simultaneously it should be taken into account whether reducing or fattening should be accomplished. The remainder of the caloric requirement is supplied by fat. Woodyatt's formula may guide us in our computation. According to this the total amount of glucose should be:

*Basic caloric requirement*

$$G = \frac{\text{Bas. cal. requ.}}{17}$$

$$D = G \times \frac{8}{10} - \frac{P}{2}$$

$$F = D \times 2 + \frac{P}{2}$$

Insulin in diabetes mellitus is a causal therapy. The cause of the pancreas diabetes is hypo-isletism, caused by any reason, with or without morbid anatomic or sometimes even microscopic changes, whereby the insulin production is impaired. The insulin administered makes up for this deficiency. Its proper administration equals a cure and should make any dietary regulation superfluous; because it corrects, respectively makes up, for all that is missing. The fact that we are advocating strict dietary regulation proves that insulin treatment is, the way it is administered today, far from being what it should be. Its technic, dosage, administration, etc., is insufficient the way it is used today. The first drawback is explained by its hypodermic administration in doses, and intervals, which do not answer the requirements, because it cannot provide the automatic regulation of the insulin production or of its liberation as it is in the case of normal individuals. If the administration of insulin

would be safe and its utilization automatic, every diabetic should get it, but under the present conditions we administer it only in the severe cases. If under a diet with the basal caloric requirement and the minimum safe amount of carbohydrates no equilibrium in weight, and especially no aglycosuria can be achieved, insulin is indicated.

It is practically not feasible that the blood-sugar reducing effect of the insulin should precisely counteract the blood-sugar increasing effect of the food ingested. If this could mathematically be arranged, no dietary treatment would be necessary. Under-dosage requires dietary regulation, over-dosage brings on hypo-glycemic reaction, which is still more dangerous. This is the Scylla and Charybdis.

Otherwise, insulin is the greatest practical discovery, maybe of this century; the number of lives actually saved goes into ten or hundred thousands. Its effect in coma—and that is the experimentum crucis—exceeds the most audacious expectations. No operative activity in any field of surgery can yield more striking results or more sudden changes.

Insulin is the causal therapy in diabetes mellitus as well as in all of its complications.

Few remarks and observations which do not fit themselves to every-day practice with insulin treatment, are:

(1) If insulin is not feasible otherwise it may be successfully administered once a day before the chief meal in the evening, the distribution of the carbohydrates being correspondingly arranged.

(2) The ratio between the number of insulin units and carbohydrate utilization may show a discrepancy; a few units of insulin being able to burn relatively more dextrose than those in larger doses.

(3) Insulin may increase the carbohydrate tolerance during and after treatment. The after-effect enables and in many cases justifies the cyclic administration of insulin for 4 to 8 weeks, followed by a few months of insulin-free treatment.

(4) Insulin may have at a later period markedly less sugar-burning power than earlier, in this way counteracting its tolerance-increasing after-effect.

(5) The same amount of insulin given for a length of time may produce quite a different effect at different stages. An amount which is the proper dose today may be responsible for a hypoglycemic reaction after a few days on an unchanged diet. This implies and necessitates in such cases the gradual decrease of the insulin dose.

(6) Sudden decrease in insulin dose may also cause a hypoglycemic reaction in special instances. Reduction of insulin units may act perhaps by over-stimulating the islet-function in the effort to keep up the same insulin concentration in the system as was present before the reduction of the insulin doses started. It may occur that while the insulin doses were being gradually increased, even though large doses of

insulin were administered, aglycosuria could not be achieved, but a few days later, in the period of gradually decreasing doses, aglycosuria set in, and perhaps, even after cessation of the insulin, continued for a certain length of time. Insulin treatment may in such cases resemble the immunization process in some respects.

(7) If we keep the patient on a rather strict diet with nicely adjusted insulin doses, not much carbohydrate accumulation can take place in the system, and the insulin administered will promptly oxidize the carbohydrates available, i.e., the carbohydrates ingested. If we give relatively large doses of insulin with a larger amount of carbohydrates especially if both or either of them are administered in increasing or decreasing doses, postponement, after-effect, accumulation, delayed response, etc., may easily occur; in one case resulting in the insulin assuming some part of the pancreas function, and at a later date in its reduction or cessation overstimulating the arrested islet function; or, the insulin given in excess may deplete the glycogen deposits and the dextrose in the blood and tissues, and, while previously even larger doses did not completely consume the carbohydrates ingested on account of their being engaged in combating the glycogen, the tissue and blood-sugar; after their oxidation the same and even smaller doses applied exclusively for oxidation of the carbohydrates ingested may, with the same carbohydrate intake induce complete aglycosuria or even a hypoglycemic reaction, when a few days before even larger doses were unable to do so.

The function of the islets seems—at least to a great extent even in cases of very severe diabetes—only to be suspended, functionally disturbed, and not totally lost. After a rest, due to reduction of the carbohydrates in the food and to a preceding insulin cure, whereby insulin assumes the not entirely lost function of the islets, the latter can and do produce insulin again in an unexpected concentration.

I will not close the topic of the treatment of diabetes mellitus without mentioning the experimental work done by G. Mansfeld who performed a partial Steinach's operation on the pancreas of the dog. He produced after ligation of one of both pancreatic ducts overproduction of insulin, and proliferation, hyperplasia and hypertrophy of the respective Langerhans' islets while the other pancreatic duct remained untouched, carrying the essential and ferments-containing, outer-secretory products, supplied by the intact portion of the pancreas. In case only one pancreatic duct was present he dissected the pancreas into two parts and ligated the one, care being taken for their blood-vessel supply; while the one portion preserved both the external and internal secretion, the other, being deprived of its external secretion, became destined for the prospective hyperplasia or its Langerhans' islands. Whether and how this idea will gain access in the human pathology remains an open question at this time.

# Malaria in Legal Medicine—Cases in Relation With Accidents

By Ricardo Aguilar, B.S., B.A., D.D.S., M.D., F.A.C.P.,
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EXPERIENCE has taught employers of labor to take into consideration various conditions such as alcoholism, epilepsy, syphilis, diabetes, nephritis, etc., as causes for rejection, particularly in filling positions when danger and responsibility are involved.

Any of these conditions may be responsible for temporary aberrations or loss of consciousness, and lead in some instances, to serious loss of life and property.

In this connection, malarial infections have not been considered, but as shown by the following case reports may at times be responsible for serious accidents with subsequent medico-legal action and unjustifiable penalties against employers or corporations that are in no way responsible. In many of these cases the individual employees are at fault and not the employer.

When an employer presents every known means to an employee to prevent malarial infection, and the necessary agents and instructions for his cure, the former should not be held responsible for the neglect of the latter who does not profit by the instructions given him.

In all cases where accidents occur a careful physical examination should be made of the combination concerned, supplemented by laboratory findings, and a report with a complete diagnosis furnished the Judge in order to enable him to reach a just conclusion and fix responsibility.

The proneness of malarial infection to produce delirious and other cerebral conditions whereby consciousness is lost and responsibility ceases, places this disease in a similar category to alcoholism, epilepsy, diabetes, etc. There are two type of cases: one is the type in which malaria in an employee to others, is the cause of an accident, and the other is the increase of severity of traumatism in an individual case, on account of malaria infection.

*Case* No 1—O. F. native, 19 years old. Admitted to Hospital on May 14, 1927. Patient had been with fever for two days. Patient was on duty as fireman on a special train and developed suddenly a chill followed by a severe attack of fever. In Gualan (a small Railroad Station on the line) the engineer on the train went for lunch, and my patient without any instructions started the engine and ran the train to the next station. Fortunately the other members of the train crew succeeded in reaching the engine and it was stopped at the following station. Patient was under arrest but later was brought to Hospital on the authorities finding placed that he had a severe attack of fever. This incident

luckily did not cause accident but it might had been the cause of a serious wreck on the line, as the fireman started without any "via" or orders from the train dispatcher.

On admission temperature was 103, pulse 96, skin pale, with profuse perspiration. Tongue coated, liver tender, spleen palpable and tender. Patient was delirious. Blood was positive for E. A. Malaria parasites.

Diagnosis: E. A. Malaria (Cerebral Type).

After two days of VIII minims of adrenalin and 15 grains of quinine hypos b.i.d. temperature became normal and complete relief of symptoms was noted.

*Case* No. 2—M. H. native, soldier, 24 years old, admitted to Hospital on July 23, 1928. His right leg was struck by a falling timber while a hurricane swept over a village.

Working Diagnosis: Compound fracture of right tibia.

On admission patient was extremely postrated and shocked, with high fever, heart rapid and weak, lungs negative, abdomen slightly distended, right leg undue motility, and severe fractures of both bones, two inches above ankle, showing a site puncture wound of skin, which had bled freely. No evidence of fracture infection.

Diagnosis: Compound fracture of right tibia; Clinical Malaria (Cerebral Type).

Patient died on second day after admission and had temperature of 105 and 106 for the two days in Hospital.

*Case* No. 3—W. W. American negro, engineman. Felt very ill while on engine this morning. On arrival at Quirigua left his passenger train engine and reported to Hospital for consultation, and medicine, intending to continue on his engine and finish his run.

He was palpably too ill to be trusted on an engine, and he was persuaded to remain in Hospital, and tie up the train until another engineer could be sent to take charge of it.

Paient had been ill for three days and taken treatment outside.

Patient vomited shortly after arrival in Hospital, perspired profusely, became nauseated, and went into condition of collapse. Severe diarrhea and vomiting supervened.

Diagnosis: Clinical Malarial (Algid Type).

If this man had continued on his run it is quite probably that an accident might have occurred, giving a medio-legal problem.

# Adrenalin in Malaria

By Ricardo Aguilar, M.D., F.A.C.P., D.D.S., *Quirigua Hospital, United Fruit Co., Puerto Barrios, Guatemala*

I KNOW of no literature regarding the use of adrenalin in the treatment of pernicious malaria but have noted the beneficial clinical results obtained by Doctor N. P. Macphail, who has used it rather extensively in cases of persistent nausea and vomiting incident to severe malaria infection.

In pernicious attacks, whether of the cerebral, algid or paratyphoid types, sluggish reactions from the use of quinine, intramuscularly, or orally, supplemented by subcutaneous injections of adrenalin chloride in doses of from 8 to 15 minims, it is frequently followed by an acute exacerbation of the symptoms; and though parasites could not be previously found in the peripheral blood, they appeared subsequently in comparatively large numbers, and the sequence of events, in the clinical condition and prompt recovery of the patient was most gratifying.

Apparently the adrenal injection caused a constriction of the blood vessels, spleen and other homoiopoetic organs, and forced the parasites into the circulation, relieving pre-existing stasis or loss of vascular tone.

Keeping in mind these observations I began to use the adrenalin injections in all cases of pernicious malaria irrespective of the type or the localized character of the clinical symptoms and herewith present a few brief cases that will illustrate the prompt results obtained.

It may seem curious to the reader to note that in about one half the number of cases reported parasites were not obtained in the periphereal blood. This can be accounted for as follows: In this Division the cases come from the camps which are inspected daily and all those suffering from fever are promptly given quinine in large quantities before they are forwarded to Hospital for treatment. It is well known to all malariologists, accustomed to deal with E. A. Malaria, that when the parasites are about 18 hours old, they are caught in the deep viscera, and although the peripheral blood may have contained enormous number of parasites when the blood was examined, a smear taken a couple of hours subsequently may fail to reveal parasites or comparatively few may be found.

*Case* No. 1—E. U. (Cerebral Psycopathic Type), native, female, 18 years old, admitted to Hospital on May 1st, 1928.

She had complained of severe headache on returning from School, and was seized with a form of cerebral attack, and became delirious, in which condition she entered the Hospital. Temperature was 102,

pulse 120, respiration 24, and she suffered from incontinence of urine. Her blood was positive for E. A. Malaria. For three days the patient was given quinine intramuscularly, .15 grains every 6 hours, supplemented with bromides, without relief. On the fourth day XV grains of quinine administered instramuscularly 20 minutes after an injection of six minims of adrenalin chloride solution in the morning and repeated at noon. Spinal puncture was performed and 20 cc. of spinal fluid removed, with a hemolytic solution as though an old clot dissolved in the spinal fluid. Next day the patient was much improved, had been bright, but quinine hypo and adrenalin was given morning and noon, as well as the following day. On the 7th day temperature and pulse were normal, adrenalin and quinine hypos were discontinued and 10 grains of quinine administered orally were given. Patient discharged in good condition on May 15th.

*Case* No. 2—M. N. L. native, male, 13 years old, admitted to Hospital May 19, 1928. (Cerebral type). Unconscious and history was not obtainable. Temperature was 104, pulse 144 and respiration 40. Vomiting and delirious. Eyes show nystagmus. Blood was positive for E. A. Malaria parasites and urine showed traces of albumin. Patient was given 10 grains of quinine intramuscularly repeated every six hours and digitalin 1/100 hypo. Hot water bags, blankets, and ice cap to head. Next day patient was still unconscious and temperature was 103¼, pulse 144. Adrenalin minimus V hypo, and 10 grains of quinine intramuscularly morning and night. Spinal puncture was made and 15 cc. of clear transparent spinal fluid removed with normal pressure; but after 15 cc. had been removed, blood appeared in the fluid, which demonstrated that there was acute congestion of the cerebral blood vessels. After the administration of adrenalin and quinine hypodermically, temperature and pulse became normal and complete relief of symptoms were noted. Patient was discharged on May 31st in good condition.

*Case* No. 3—F. H. native, male, 30 years old (Cerebral Type). Admitted to Hospital on April 13, 1927, unconscious and history was not obtained. Temperature was 102, pulse 92, respiration 20. Delirious and with nystagmus and positive Kernig. Blood was negative for malaria parasites. Patient was given 22½ grains of quinine hypo twice daily and no relief of symptoms were observed. On the second day seven minims of adrenalin following by 15 grains of quinine hypo were given morning and noon, after which patient became conscious, with normal temperature and pulse. Patient was discharged on the 20th of April in good condition.

*Case* No. 4—S. R. native, male, 12 years old, (Cerebral type) admitted to Hospital on May 23rd, 1927. Unconscious and history was not obtainable. Temperature was 99, pulse 120, delirious, and blood was negative for malaria parasites. Skin and conjunctivae pale and nystagmus, distended abdomen, enlarged spleen, positive Kernig. Patient was given 5 minims of adrenalin and 7½ grains of quinine hypo. Twice daily for the first and second day with excellent results. On the third day quinine was administered orally. Patient discharged in good condition on May the 1st.

*Case* No. 5—W. C. American negro, 45 year old (Algid Type). Admitted to Hospital on July 19, 1928. Patient had been under treatment for malaria for three days but felt worse the morning of admission. Profuse perspiration, cold skin, profuse diarrhea and vomiting. Admitted to Hospital in a collapsed condition. Temperature was 96, pulse 90 and thready. Blood was negative for malaria parasites and urine showed traces of albumin. Patient was given a minim of adrenalin chloride solution hypo. whisky ½ oz. every four hours, blankets, hot water bags, etc., followed by 15 grains of quinine intramuscularly on admission, repeated in six hours. Complete relief was noticed in 12 hours, and the following day quinine was administered orally until he was discharged in very good condition on the 29th of July.

*Case* No. 6—M. R. B. male, Portuguese, 33 years old. Admitted to Hospital on July 22, 1928. Patient had fever and chills, tongue. Hepatic and spleenic areas tender on pressure. Blood was negative for malaria parasites.

Patient was under quinine routine combined with plasmochin for six full days running daily temperature of 101 and 102. 15 grains of quinine hypo was administered twice daily for two days without any results, until 8 minims of adrenalin and 15 grains of quinine hypos. was given. Temperature went up to 104, pulse 112 with a crisis of chills; an hour after temperature and pulse were normal and complete relief of symptoms was noted. Patient was discharged on August 3rd in good condition.

*Case* No. 7—F. C. native, male, 26 years old, admitted to Hospital on May 20, 1927. Patient had fever and chills daily, anorexia, nausea for six days. Nutrition poor, skin pale, coated tongue, liver tender at G. B. region, spleen enlarged and tender. Blood was negative for malaria. Patient was given 15 grains of quinine hypo twice daily without any relief. Eight minims of adrenalin followed by 15 grains of quinine hypo was given twice daily for two days, relieving all symptoms. Patient discharged in good condition on May 30th.

*Case* No. 8—G. T. native, male, 25 years old, admitted to Hospital on February 26, 1928. Fever and chills daily, headache and nausea for four days. Skin pale, jaundice, tongue coated, eyes with jaundiced sclera, hepatic and spleenic regions tender on pressure, enlarged spleen, blood negative for malaria, temperature 103, pulse 120.

Upon examination on the following day there were E. A. malaria parasites in his blood. Patient had been under quinine treatment for two days without any relief of symptoms, and temperature was still high. 8 minims of adrenalin and 15 grains of quinine intramuscularly were administered and relieved all symptoms. Patient discharged from Hospital in good condition after six days treatment.

*Case* No. 9—J. C. male, native, 17 years old (Cerebral Type) admitted to Hospital on May 23, 1928, in an unconscious condition. Skin warm and moist, heart and lungs O. K. spleen palpable and tender, limbs negative, asthenic and weak, vomiting and delirious. Temperature 103, pulse 140, blood positive for E. A. malaria parasites about 50 per field (thick film). 15 grains of quinine hypo proceeded by 10 minims of adrenalin hypo relieved all symptoms, on the second day temperature was normal. This treatment was followed by quinine and plasmochin tablets by mouth. Patient discharged in good condition after eight days treatment.

Those case reports are representatives of a large number of cases which have been treated in the same manner during the past two years. I believe that the use of adrenalin in conjunction with quinine in the treatment of serious cases of malaria deserves further study.

# Editorial

## *THE FUNCTION OF THE ADRENAL CORTEX*

In the higher animals the adrenals consist of two forms of tissue differing widely in their structure, genesis and function, the cortex and the medullary portion. It has been generally accepted that the medulla is the place of production of adrenalin, and that this substance is produced also in other glandular systems closely related to the sympathetic nervous system. But with the acceptance of this fact our knowledge of the general function of the adrenals is exhausted. It would seem logical that the physiology of both tissue complexes must represent an *entity* corresponding to the anatomical concentration of the two tissues. But nothing is known of the function of the cortex. The present day conceptions of the physiologic activity of the cortex fall into three categories. The first of these indicates the rôle of the adrenal as a detoxicating organ. This view is supported experimentally and pathologically by various facts, in part by the occurrence of a susceptibility to poisons of the body in adrenal insufficiency, and in part by adrenal reactions on the appearance of an organ insufficiency or defect resulting from the introduction of poisons into the body. It has been assumed by some workers that the lipoids of the cortex, particularly cholesterin, act as a kind of neutralizing substance, in the same manner as the last-named precipitates digitonin; by others it is assumed that the poisons circulating in the body fluids are "magaziniert" by the adrenal cortex. The second category is based upon the appearance of the cortical cells under varying conditions. The French School, together with some Russian and German workers hold the view that the essential function of the adrenal cortex is the production of lipoids, particularly cholesterin, for the needs of the body. Against this view is opposed that of the Aschoff School who claim that the adrenal cortex produces neither cholesterin or cholesterin-ester, but on the other hand is simply infiltrated by these substances when they are admitted to the body. This view does not include the denial that the adrenal cortex possesses an up to the present time unknown secretory function. Certain authors holding fast to the idea of the adrenal as a detoxicant organ compromise with regard to the two views given above, in that they believe that the adrenal secretion neutralizes the circulating poisonous material. The third view rests essentially upon the assumption that the adrenal cortex secretes a hormone more or less of general importance to the whole body. Falta and Stephan support this view. Goldzieher, who formerly held the extreme view that the most important

function of the adrenal was that of the medulla, while the cortex was relatively without significance, now believes (1928) that he has isolated a cortical hormone, "nerihormone" with specific action. A hormonal action of cortical extracts had been earlier observed (Kűhl, 1926). Further, Goldzieher used rats as his experimental animals, which are the least adapted for the study of the phenomena of cortical insufficiency, since in fifty per cent of these animals accessory adrenal tissue is present, so that it is impossible to be sure that all adrenal cortical tissue is removed in any given case. Alsterberg (1928) has studied the adrenal cortex by means of a new impregnation-method devised by him. By means of this method he has been able to demonstrate the presence of lipoids in the capillaries of the adrenal cortex which he regards as the true hormonal secretion of the cortex. He concludes that the adrenal cortex secretes as hormone just that lipoid substance which enters into the mitochondria of the cells and into all cell structures. The function of the adrenal becomes in this way of general significance, it is a regulator of the activities of the individual cells. While other hormone effects are specific, that of the adrenal cortex is general and difficult to define. Its significance is best shown in the reactions of the different organ-systems in adrenal insufficiency. Destruction of the adrenal cortex leads to death of the animal if accessory tissue consisting of adrenal cortex is not present. Further it is very striking that the temperature regulation is disturbed in great degree and that the temperature of the animal falls below normal. This regulation is to a high degree a cellular property and its insufficiency is also such. The general muscle weakness is also striking, which shows that the muscle cells are severely altered. It is of great interest in this connection that injections of cortical extracts are able to offset the extreme muscle weakness which occurs in adrenalectomized animals on the slightest bodily exertion. Likewise, the psychical apathy, and changes in the irritability and conductivity of the nerves, the rapid and extensive emaciation, the lowering of metabolism, the disturbances in digestion, defective excretion, the accumulation of poisons, the pigmentation of the skin, occurrence of abortion, etc., all of the pathology of adrenal insufficiency indicates the involvement of the entire organism. According to Alsterberg *adrenal insufficiency means a cellular insufficiency; in hypofunction of the adrenal cortex there occurs a general hypofunction and in adrenal hyperfunction a general cellular hyperfunction.* The adrenal cortex stands in close cellular relationship to every organ so that insufficiency of a single organ is followed by regulatory reactions in the adrenal cortex. Alsterberg further holds that the function of the adrenal medulla and of adrenalin is to act as regulators for the transport of the cortical lipoids. The same influences which act on the secretory activity of the cortex act also on the production of adrenalin by the medullary substance. In favor of this view are the anatomical relationships of the medulla to the sympathetic nervous

system and the intimate relationship of the medulla to the cortex. Alsterberg believes that it is possible that the cortical secretion consists of one or more phosphatids. In the Goldzieher hormone phosphoric acid was wanting. The adrenal secretion does not consist of cholesterin, in this regard the Aschoff school is right. But the secretion is without doubt to be regarded as a lipoid, eventually it forms a combination of lipoid and albumin, which agrees with the finding by Ciacco in the cortical capillaries of a fuchsinophile substance. Off and on has the view been advanced that the adrenals regulate the presence of phosphatids in the body, eventually through a production of the same. Against this belief it has been urged that in adrenal insufficiency the phosphorus content of the body remains high, even rises in the blood. This does not exclude the possibility that phosphatids already produced and given over to the cells are released and appear in the body fluids. Summing up Alsterberg's views, he believes that lipoids are given off into the cortical capillaries by the cells of the adrenal cortex. These lipoids are made use of by the lipophorous portions of the various organs and tissues. There exists a reciprocity between the secretory activity of the adrenal cortex and the functional activity of the body cells. On hypofunctional inactivity of the adrenal cortex there occurs a corresponding inactivity of the body cells, and in hyperfunction of the cortex a corresponding hyperactivity in the work and function of the body cells. In increased cell activity hyperactive reactions occur in the adrenal cortex, by lowered cell activity there occur hypoactive reactions in the cortex. It is probable that the chief function of the adrenal medulla is to serve as a regulator of the secretion and blood circulation through the cortical tissue.

# Abstracts

*The Progressive Anemia Following A Single Intra-Marrow Injection of B. Welchii Toxins.* By John C. Torrey and Morton C. Kahn (The American Journal of Pathology, March, 1929, p. 117). This study is a continuation of the authors' investigations of the anemia produced in laboratory animals by a potent *B. welchii* toxin. In a previous communication attention has been directed to the consistently and abnormally high B. *welchii* counts in stools from pernicious anemia cases. These findings have been confirmed by Davidson, although Nye believes that the difference from the normal as regards the number of *B. welchii* in the colon is more apparent than real. It was also shown that a transitory anemia with a blood picture strongly suggestive of the pernicious type in a number of features could be produced in monkeys by intravenous inoculations of such a toxin. Similar observations for rabbits have also been made subsequently by Patterson and Kast, and Barach and Draper, although these investigators consider the resulting anemia of a secondary rather than primary type. The anemia produced by actual infection of rabbits with whole cultures of *B. welchii* was earlier studied by Cornell and Reed, Orr and Burleigh, and its pernicious-like features noted. It is the experience of the authors that the morphological and tinctorial blood changes in rabbits following the intravenous inoculation of toxin, while somewhat suggestive of pernicious anemia, are not so striking as in monkeys. The present research is concerned with the effects of the toxin on bone marrow, when introduced directly into the marrow and into the blood. It has been found that the *B. welchii* is capable of producing two apparently distinct hemolysins, one of which is active both *in vitro* and *in vivo*, and the other, the more potent, causes blood destruction *in vivo* but only to a slight degree, or not at all, *in vitro*. Comparative tests of the action of these two products on bone marrow have been carried out both when introduced directly into the marrow and into the blood. As a result of this work it was found that the single inoculation of 0.5cc. of a potent sterile *B. welchii* toxin into the tibial marrow of a rabbit or monkey gives rise to a chronic, persistent and finally often fatal anemia characterized by low hemoglobin content of the blood, low erythrocyte count and a color index generally above 1.0. Anisocytosis and at times poikilocytosis are pronounced. The single inoculation of 0.5cc. of the toxin into the tibial marrow starts a degenerative process which apparently affects the whole marrow system. Definite evidence of beginning degenerative changes were noted in the marrows on the side of the body opposite the site of inoculation within eighteen hours. After twelve days the process was well advanced as shown by the marked mucous degeneration of the fat cells, great diminution in other normal marrow and blood forming cells and a marked increase in polymorphonuclear leukocytes. In rabbits which had died eleven or more weeks after the inoculation the marrows were found to be in an advanced stage of degeneration with fat cells replaced by a granular material and an extreme atrophy of the cellular elements. Nearly all the animals showed, at whatever stage examined, a rather more pronounced degeneration in marrows far removed than in that into which the toxin was injected. As intravenous inoculation of like or larger amounts of toxin causes no more than a transitory marrow injury the cause of the difference in effect is not clear. A single intravenous inoculation of *B. welchii* toxin of the same dosage or a series of increasing doses gives rise to an anemia of the

same type as that resulting from marrow inoculation but is followed within three to four weeks by an immunity and a return of the blood to normal or nearly normal condition. Such intravenous inoculation of the toxin causes some mucous degeneration of the fat cells and an increase in the cellular elements of the marrow, particularly the leukocytes, but results in nothing like the destructive action of inoculation directly into the marrow. There is as yet no experimental data to explain the difference in effects of intravenous and intramarrow inoculation, but the suggestion may be made that the undiluted toxin in its destructive action on the bone marrow with which it is brought into direct contact may give rise to secondary toxic products particularly injurious to marrow tissue, and which on absorption throughout the blood and lymph are brought into contact with all the body marrows, causing as grave an injury to those farthest removed as that into which the toxin was directly inoculated. It would seem probable that an experimental anemia produced in this way may prove helpful in the study of the treatment of pernicious anemia, particularly as regards the use of liver extracts and their standardization. It has been demonstrated by Beard, Clark and Moses that liver extract feeding to rabbits with the chronic anemia produced in this way is beneficial, resulting in a prompt and marked rise in reticulocytes, hemoglobin and red cell counts. There seems also to be a proportionality between the amount of liver extract given and the increase in number of red cells and hemoglobin content. The benefit, in fact, seems to parallel that occurring in a pernicious anemia patient on liver extract. Whipple has shown that a secondary anemia produced in dogs by repeated bleedings is only slightly benefited by feeding liver extract, although marked improvement follows the use of whole liver. It would seem, therefore, that the method of Torrey and Kahn offers a much more delicate method for potency titration. This form of experimental anemia, it is suggested, may prove a useful means for evaluating the potency of extracts of liver and other organs as blood regenerating agents.

*The Effect of Combined Feeding of Potassium Iodide and Anterior Lobe of the Pituitary Upon the Thyroid Gland.* By Howard A. McCordock (The American Journal of Pathology, March, 1929, p. 171). In a series of studies on compensatory hypertrophy of the thyroid gland Loeb has shown that the oral administration of potassium iodide in partialy thyroidectomized animals not only fails to present hypertrophy but may even stimulate regenerative activity, while the feeding of anterior lobe of pituitary gland has an inhibiting effect, preventing even moderate degrees of hypertrophy and causes a hardening of the colloid and a lowering of the acinar cells. In view of this antagonistic action of these two substances on thyroid activity in compensatory hypertrophy, it seemed interesting to see if the stimulating effect of potassium iodide would counteract the inhibiting action of anterior pituitary substance, or vice versa. The experiments in this investigation concerned the effect of such combined feeding with potassium iodide and anterior pituitary on the thyroid gland; the result of administering each of these two substances separately to different animals and a comparison of these three types with normal thyroids from control guinea pigs. From these experiments it may be concluded that the marked mitotic proliferation induced so readily in the thyroid of guinea pigs by potassium iodide is prevented by anterior pituitary gland when both are fed to the same animal. These two substances administered separately are antithetical in their action on the thyroid; anterior pituitary gland depressing proliferative and probably also functional activity as indicated by a decided drop in the mitotic count below the normal level and by the appearance of small acini with a dense deeply staining coloid, while KI. causes marked stimulation, in the initial stage of its action at least, with enormous increase in the number of mitoses and with the appearance of a softened, pale, vacuolar colloid containing phagocytic cells. The condition of the thyroid which follows feed-

ing of both these substances to the same animal is due to their direct action on the gland itself, and not an effect which they exert upon each other before absorption from the gastro-intestinal tract, because changes in the thyroid are the same whether both drugs are fed simultaneously or whether one is fed in the morning and the other in the evening precluding any chance of direct interaction between them. The stimulating influence of iodine and the depressing property of anterior pituitary substance can be balanced in such a manner that an approximately stationary or resting condition in the thyroid results. In some respects anterior pituitary substance produces changes in the thyroid gland analogous to those induced by thyroxin or thyroid itself. From these experiments it is impossible to determine the exact manner in which pituitary substance exerts its influence upon the thyroid gland. All that one can say is that in some way the oral administration of anterior pituitary tablets (Armour & Co.) causes a depression in the activity of the thyroid with a marked lowering of the number of mitoses in the gland and with the production of medium-sized, or somewhat smaller, acini distended with hard colloid compressing the living epithelium into thin strands of cells. During the first stage of its action, potassium iodide, on the other hand, produces marked stimulation with enormous mitotic activity and a slightly softened colloid occasionally containing large numbers of phagocytic cells. The early proliferative change induced in the thyroid gland by potassium iodide is prevented by anterior pituitary when both these substances are fed to the same animal.

*Likeness and Contrasts in the Hemolytic Anemias of Childhood.* By Thomas B. Cooley (Amer. Jour. of Diseases of Children, December, 1928, p. 1257). There are three diseases of early childhood, apparently rather closely related not only in symptomatology, but probably also in fundamental etiology: congenital hemolytic icterus, sickle-cell anemia and the disease which has hitherto been included under the rather vague classification of von Jaksch's anemia, or much better, as Cooley suggests under the more appropriate designation of erythroblastic anemia of childhood. In the present paper essential likenesses and differences between these three anemias are discussed. In all three conditions one must recognize either a congenital disease or a pronounced and peculiar congenital diathesis. Hemolytic jaundice and sickle-cell anemia are definitely hereditary and familial. The erythroblastic anemia is not known to be hereditary, obviously because its subjects are not known to reach adult life. Sickle-cell anemia is distinctly racial and possibly originally limited to a small section of the negro race. The erythroblastic anemia is so conspicuously more common in the Mediterranean races as to seem almost peculiar to them; while hemolytic jaundice, though more widespread than the other two, tends decidedly to be more frequent in certain regions and among certain people, and to appear only sporadically elsewhere. In other words, in all three the diathesis seems distinctly a matter of family or race. There are striking hematologic resemblance in the three diseases. Each seems to be characterized by a peculiar type of red cell. Microcytosis was recognized by Gäusslen and others as characteristic of hemolytic jaundice, and Gäusslen ascribed peculiar qualities to these microcytes. No other disease shows uniformly at its height so many erythroblasts as does erythroblastic anemia and after splenectomy their numbers are remarkable; Cooley regards them as a special form of cell. Hemolytic jaundice is said to show more reticulated red cells than any other disease. There is, however, but little difference in this respect between it and the other two; sickle-cell anemia especially in the active stage showing extremely large numbers. Increased fragility of the erythrocytes to hypotonic salt solutions is generally recognized as a cardinal symptom of hemolytic jaundice. It is more common in this disease but occurs also in the other two. Urobilinuria, also, more common in hemolytic jaundice, may be present in either of the others. As to the white cells, hemolytic jaundice and sickle-cell anemia do not show any remark-

able characteristics. On the other hand erythroblastic anemia, the most serious and rapidly progressing, early shows evidence of pronounced bone-marrow irritation, which apparently is reflected in the production of increased numbers of leukocytes with the appearance in the blood of early forms. With the development of marked marrow hyperplasia the number of these cells may run to high figures. The extreme hyperplasia of the marrow characterizes erythroblastic anemia; it is less constant and less pronounced in sickle-cell anemia, and has not been especially noted in hemolytic jaundice. The behavior of the spleen in the three conditions shows both resemblances and differences. In all it must be assumed to have an active part in the hemolytic process, and it is probable that the histologic changes that take place in it are somehow the result of this activity. It is rather peculiar, then, that there should be such differences as may be noted in its size and structure. In hemolytic jaundice it is often little, if at all, enlarged, and is likely to vary in size with the amount of hemolysis going on, being particularly noticeable during the crisis. Histologically it shows a moderate fibrosis and an infiltration with erythrocytes. Sickle-cell anemia has similar crises and similar changes in the volume of the spleen. In this disease the spleen is early enlarged, but later shrinks to less than normal size, with the development of a peculiar fibrosis, amounting almost to cicatrization. When removed early its gross appearance is hardly distinguishable from that seen in hemolytic jaundice. In erythroblastic anemia the early enlargement is much greater than in the other two, and the increase is progressive, with less variation from time to time. The histologic changes here are rather more complex than in the other two. Removal of the spleen has different results in the three diseases. In hemolytic jaundice, with the exception of rare cases of the pernicious type, the result is usually almost, if not quite, a complete cure. Without any remarkable immediate reaction, hemolysis stops or is greatly diminished, the anemia and the jaundice disappear and the patient is apparently well. In sickle-cell anemia after early splenectomy, there is also no pronounced immediate reaction. The patient seems somewhat improved, the anemia is less pronounced, but hemolysis is still observed, and the sickling is unchanged. In erythroblastic anemia splenectomy is followed by a remarkable increase of erythroblasts in the blood, lasting over years, and there seems to be little definite improvement in the patient. Hemolysis and jaundice, if present, may be temporarily lessened, but they return and the disease process continues as before. Cooley suggests that these three diseases might be thought of as three types of hemolytic jaundice, each dependent on a congenital diathesis, and each strikingly limited to familial or racial groups. Each is characterized by a peculiar, abnormal type of red cell, and much of the clinical symptomatology is due to hemolysis of these abnormal cells under the influence of the spleen and its associated tissues. Either physical or chemical abnormalities in all structures might be the reason for this increased susceptibility to hemolysis. As to the nature of these structural defects we possess no positive knowledge. A toxic theory could hardly have any application. Congenital abnormalities in the bone marrow is a plausible explanation and cannot at present be ruled out. Another possibility is that the failure of the bone marrow may result from an inadequate supply of proper material for blood-making, due to defective absorption or to some failure in the intermediate metabolism, whether or not due to a hormone deficiency.

# Reviews

*An Index of Differential Diagnosis of Main Symptoms.* By Various Writers. Edited by Herbert French, C.B.E. (Military), M.A., M.D. Oxon., F.R.C.P., London. Physician to H. M. Household; Physician and Lecturer, Guy's Hospital; Consulting Physician to Queen Alexandra's Military Hospital, Millbank. Fourth Edition. 1171 pages, 701 illustrations, 179 figures in color. William Wood and Company, New York, 1928. Price in cloth, $18.00.

This work has been revised throughout, but its general principles remain the same as in the first edition. Over 30,000 copies of the previous editions have been sold, and the work has been translated both into Italian and Spanish. The book is a treatise on the application of differential diagnosis to all the main signs and symptoms of disease. It aims at being of practical utility to medical men whenever difficulty arises in deciding the precise cause of any particular symptom of which a patient may complain. It covers the whole ground of medicine, surgery, gynecology, ophthalmology, dermatology and neurology. It deals with diagnosis from a standpoint which is different from that of most textbooks, being an Index of Diagnosis, in that its articles on the various symptoms are arranged in alphabetical order; at the same time it is a work upon differential diagnosis in that it discusses the methods of distinguishing between the various diseases in which each individual symptom may be observed. Whilst the body of the book thus deals with symptoms, the general index at the end gathers these together under the headings of the various diseases in which they occur. Especial stress is laid upon the importance of using these two parts of the book together. The guiding principle throughout has been to suppose that a particular symptom attracts especial notice in a given case, and that the diagnosis has to be established by differentiating between the various diseases to which this symptom may be due. Treatment, pathology and prognosis are not dealt with except in so far as they may bear upon differential diagnosis. The book is unique in medical literature in principle and in its working out. The great demand for previous editions would indicate its utility to the medical profession, and it is hoped that the present edition will prove to be of as much service as its predecessors.

*Report of the International Conference on Cancer.* London, 17-20th July, 1928. Held under the auspices of the British Empire Cancer Campaign. 588 pages. William Wood and Company, New York, 1928. Price in cloth, $12.00.

This volume contains the addresses and abstracts of papers presented at the International Conference on Cancer held in London last July. These are grouped under the general heads: Etiology of Cancer; The Relative Values of Surgery and Radiation in the Treatment of Cancer; Methods of Treatment by Chemotherapy; Occupational Cancer; Early Recognition and Treatment of Cancer of the Stomach; Sarcoma of Bone; Cancer Cachexia; Cancer of the Lung; Diagnostic Methods in Relation to Cancer; Effects of Radium and X-Rays on the Blood, Vascular and Lymphatic Systems, with Special Reference to Malignant Growths; Biological Effects of Radium and X-Rays; Geographical and Racial Prevalence of Cancer; Public Action in Regard to Cancer. The work of this Conference is distinguished chiefly by its sterility of new ideas. Nothing new of importance was presented before it; and most of the papers consisted of a rehashing of old material. Nevertheless there is a cer-

tain value in this collection of material representing the collective cancer knowledge of the day, and this volume forms a convenient resumé of most of the lines of cancer thought and work of interest to present day workers. That it leads to nowhere is not so much the fault of the workers along these lines as it is the complexity and difficulty of the problem. Cancer investigation has again reached a blank wall against which it is bumping its head. The geneticists are squabbling over dominance and recessiveness; the adherents to the theory of specific infection are silenced; The Gye-Barnard bubble has been pricked, the colloidal lead treatment discredited and conservatism is asked for in the radium and x-ray treatment of cancer. Nevertheless, this volume contains much of great value, particularly with reference to occupational cancer. It is a well-printed volume.

*Methods and Uses of Hypnosis and Self-Hypnosis. A Treatise on the Powers of the Subconcious Mind.* By Bernard Hollander, M.D., M.R.C.S., L.R.C.P. 191 pages. The MacMillan Company, New York, 1928. Price in cloth, $2.50.

This book is the result of thirty years' experience of experimental hypnosis and hypnotic treatment. Its main object is to draw attention to the importance of hypnotism and its phenomena in order to stimulate inquiry into what is still a mysterious and unexplored subject. Suggestion plays a very important part in our mental development, and in our intercourse with our fellows. No one can escape its influence. We are constantly receiving suggestions, or suggesting to others, though we are not always conscious of the power we are exercising. In hypnosis suggestibility is greatly increased. All hypnotic phenomena cannot be explained by suggestion, and certainly do not depend entirely on it, but can be produced without its influence. It is shown in this book that, contrary to common belief, sleep is quite unnecessary for the induction of hypnosis. In the author's opinion the wonderful phenomena produced in the hypnotic state depend on the bringing into prominence of what is termed the subconscious mind, and utilizing it for practical ends. This state resembles that in which men of genius have achieved their highest creations, while completely oblivious of their physical sensations and external surroundings. In this state of passive concentration, when no impression from the external world reaches the brain, the mind can be directed to the bodily functions and extraordinary physiologic results obtained —results leading to spontaneous and lasting cures. Such hypnotic treatment is peculiarly successful in nervous and mental disorders and moral failings. To make the cures lasting it is absolutely essential to re-educate the patient—a task which, in the hypnotic state, is far easier to accomplish than in the waking state. Further, it is shown in this book that the study of hypnotic phenomena brings us nearer to an explanation of such mysterious manifestations as Thought Transference, Clairvoyance, Premonitions, etc. Hypnotism is no longer a matter for the showman, but for the physician and the psychologist. This book should help educated people to learn something of its facts. The author hopes that the records given will convince the reader that there are forces in human beings the presence of which, with our available knowledge, we can only surmise, and that the strange powers of hypnosis may unlock many doors and lead to the solution of many mysteries.

*Handbook of Physiology.* By W. D. Halliburton, M.D., LL.D., F.R.C.P., F.R.S., Emeritus Professor of Physiology, King's College, London; and R. J. S. McDowall, M.B., D.Sc., F.R.C.P. (Edin.), Dean of the Faculty of Medicine and Professor of Physiology, King's College, London. Eighteenth Edition. 902 pages. 500 illustrations, 3 colored plates. P. Blakiston's Son and Co., Philadelphia, 1929. Price in cloth, $4.50.

Halliburton's Physiology has seen seventeen editions in twenty-nine years, a total of 116,000 copies. When in 1928 another revision became necessary, Professor Halliburton found that he needed help in preparing it, his successor Professor McDowall

was secured, and the latter's name has been added to the title of the book. There has been considerable rearrangement, both in the order of the chapters and within the chapters. Some have been rewritten, particularly many of the Nervous System, so as to bring Reflex Action up-to-date, and to admit of adequate treatment of Postural and Conditional Reflexes. The sections on the Autonomic Nervous System, the Control of the Circulation, the Carriage of Carbon Dioxide, the Maintenance of Body Neutrality, Vitamins, Ductless Glands, and Intermediate Metabolism are also for the most part new. Additions have been made on the following subjects: the Formation of the Blood and the Bile, Test Meals, Blood Groups, the Polygraph, recent work on the Spleen and Control of Respiration, the effect of Exercise on Respiratory Exchanges, and various other matters. To admit this new material anatomical detail has been reduced, but essential anatomy and physiologic histology have been retained. Many new diagrams have been added. Particular stress has been laid on the requirements of the medical student by omitting less essential details and emphasizing principles. The book has actually been reduced slightly in size. This edition of this classic textbook appears to be fully brought up-to-date. It retains the good qualities of the older editions in its clear and concise treatment of physiologic structure and function.

*Applied Bacteriology for Nurses.* By Jean Martin White, R.N., Instructor in Sciences, School of Nursing of St. Mark's Hospital, New York City; Formerly Visiting Instructor, Schools of Nursing of Bellevue and Harlem Hospitals, New York City. 200 pages, 44 figures. The MacMillan Company, New York, 1928. Price in cloth, $2.25.

It is difficult to select from a field so wide as that of Bacteriology the facts and principles with which the nurse must become familiar, since her work is not that of the bacteriologist or the technician. To her is delegated the important task of correlating the discoveries of the laboratory with the routine of the ward and the technique of the operating room. This textbook is offered in an attempt to simplify this work of selection and application; and an effort has been made to set forth the essential facts in a way in which they may be easily understood and to show how this knowledge may be used. The subject is treated in sixteen chapters comprising an Introduction, Plants Independent and Dependent, General Characteristics of Bacteria, Non-pathogenic Bacteria, Collecting of Pathological Specimens, How Bacteria are Studied, How Bacteria are Destroyed, Bacterial Activities in the Human Body, Bacteriology and Nursing Technique, Bacteriology in Surgery, Theories of Immunity, Application of Immunity Theories, Water and Milk, Important Pathogenic Cocci, Important Pathogenic Bacilli, and Other Important Pathogenic Organisms. These chapters set forth the essential facts in a way in which they can be easily understood, and show how this knowledge can be used. It is a satisfactory book for the purpose for which it is intended.

# College News Notes

Lieutenant-Colonel Edward G. Huber of the U. S. Army Medical Corps was elected President of the honorary public health society, Delta Omega, at its fifth annual meeting in Chicago last October, during the convention of the American Public Health Association.

The Delta Omega Society now has about two hundred members belonging to six chapters at the Johns Hopkins School of Hygiene and Public Health, the Harvard University School of Public Health, the Massachusetts Institute of Technology, the University of Michigan, the Yale School of Medicine and the University of California.

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Dr. Bernard Fantus (Fellow), Detroit, was elected Chairman of the advisory council of the League for the Prevention of Hay-Fever at a recent meeting.

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Dr. Anton J. Carlson (Fellow), Professor and Chairman of the Department of Physiology, University of Chicago, spoke before the Chicago Medical Society February 13 on "Attempts to Stimulate Physiologic Processes by Diathermy."

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Dr. Karl F. Eschelman (Fellow), Buffalo, and a staff of fourteen physicians will conduct a cancer clinic at the Buffalo City Hospital each Saturday morning. The clinic will have a small supply of radium at its disposal.

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Dr. George Morris Piersol (Fellow), Philadelphia, addressed the Buffalo Academy of Medicine, section of medicine, February 13 on hemorrhage from the gastro-intestinal tract.

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Dr. Albert H. Hoge (Fellow), Bluefield, West Virginia, addressed the Cabell County Medical Society recently on "Hypothyroidism."

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Colonel Bailey K. Ashford (Fellow), U. S. Army, retired, now Professor of Tropical Medicine and Mycology at the University of Porto Rico, represented the United States at the First International Conference on Tropical Medicine and Hygiene at Cairo, Egypt, in December.

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Dr. E. B. Krumbhaar (Fellow), Philadelphia, is President of the Rush Society of the University of Pennsylvania.

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Dr. Carl V. Vischer (Fellow), Philadelphia, a member of the medical staff and Lecturer on Medical Nursing at St. Luke's Hospital is Co-Author with Ruth D. Smathers, B.S.; Dietician; and Mary A. Moran, R.N., of a small book on Diets. The book should serve as a valuable guide to physicians when ordering the commonly used diets.

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Dr. Arthur C. Morgan (Fellow), Philadelphia, has been appointed Chairman of the Disabled Soldiers and Medical Aid Committee of the Philadelphia County Council, American Legion. This appointment is one of the most important posts in the Council.

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Dr. Charles D. Aaron (Fellow), Detroit, Professor of Gastro-Enterology and Dietetics at the Detroit College of Medicine and Surgery, is author of a book, "Diseases of the Digestive Organs," published by Lea and Febiger, Philadelphia.

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Dr. S. Calvin Smith (Fellow), Philadelphia, delivered a lecture, "Hints on Heart Health," the first of a series of health and

economic talks at the Philadelphia County Medical Society on February 5.

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Dr. Adolph H. Nahman (Fellow), San Francisco, on February 1, 1929, was appointed Chief of the Medical Clinic and Associate Chief of the Medical Department of the Mount Zion Hospital, of San Francisco.

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Dr. Paul F. Whitaker (Fellow), Kinston, presented a paper on "The Treatment of Duodenal Ulcer" before the recent meeting of the Seaboard Medical Association at Washington, N. C.

Dr. Whitaker was elected President of the Lenoir County Medical Society for the ensuing year at a meeting on February 10.

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Dr. A. R. Foss (Fellow), Missoula, has been ill since August, 1928, with septic gallbladder and subdiaphragmatic abscess. He is convalescing now in Hollywood, Calif., and expects to resume his practice soon.

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Dr. Samuel Ayres, Jr. (Associate), Los Angeles, on January 23 addressed the Pacific Physiotherapy Association (Los Angeles) on treatment of skin diseases by light therapy.

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Dr. Edwin G. Bannick (Fellow), Rochester, Minnesota, spoke on "Nephritis" before the meeting of the Iowa and Illinois Central District Medical Association, January 17, at Davenport.

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Dr. LeRoy Crummer (Fellow), Omaha, addressed the San Francisco County Medical Society, February 5, on "The Necessity of a Fad."

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Dr. William F. Cheney (Fellow), San Francisco, was elected President of the Commonwealth Club of California for the ensuing year.

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Dr. Emanuel Libman (Fellow), New York, donated a gift of $10,000 to the Johns Hopkins University for the establishment of a lectureship in the history of medicine, to be named the Hideyo Noguchi Lectureship.

Dr. Edwin L. Gardner (Associate), Minneapolis, is Secretary of the Minneapolis Society of Internal Medicine. This Society recently announced its third annual prize of $250 to be awarded "to the practicing physician, exclusive of members of this society, in the state of Minnesota who has been deemed most worthy to receive a prize in research in clinical medicine."

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Dr. Horace W. Soper (Fellow), St. Louis, recently addressed the Jackson County Medical Society (Kansas City) on constipation.

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Dr. Edward E. Cornwall (Fellow), Brooklyn, was one of the speakers at a symposium on pneumonia at the meeting of the Medical Association of the Greater City of New York, February 18.

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Among the speakers at the symposium held, February 26, by the Pittsburgh Academy of Medicine on the aims and accomplishments of organized medicine were the following members of the College: Dr. Thomas G. Simonton (Associate), President of the State Medical Society and William H. Mayer (Fellow), former President of the Allegheny County Medical Society.

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Dr. Arthur C. Morgan (Fellow), Philadelphia, recently addressed the Harrisburg Academy of Medicine on cardiorenal disease.

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Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, addressed the Montgomery County Medical Society, January 18, at Dayton on the modern treatment of anemia.

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The Chi Zeta Chi Medical Fraternity, founded at the University of Georgia School of Medicine in 1903, celebrated its twenty-fifth jubilee at St. Louis, December 28-30. Having been exclusively located in southern medical schools, the fraternity decided to consider petitions from medical schools

in the north, east and west, and Dr. Thomas Noxon Toomey (Fellow), St. Louis, was elected supreme eminent master.

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At the annual meeting of the Radiological Society of North America in Chicago, December, 1928, Dr. Maximilian J. Hubeny (Fellow) was elected President.

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Dr. Robert M. Moore (Fellow), Indianapolis, on February 5 addressed the Summit County Medical Society at Akron, his subject being "Some Consideration in Heart Failure of the Anginal Type."

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Dr. McKim Marriott (Fellow), St. Louis, and Dr. Julius H. Hess (Fellow), Chicago, were members on the faculty of the Graduate Course in Pediatrics for practitioners, which was given at the University Hospital in Oklahoma City, February 11-15, and arranged by the University of Oklahoma School of Medicine and the Extension Division.

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Dr. Irving Gray (Fellow), Brooklyn, Associate Attending Physician at the Jewish Hospital, has been placed in charge of a newly created department of Gastro-Enterology at the same institution.

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Dr. Hubert Work (Fellow), Colorado Springs, Secretary of the Interior during most of the administration of President Coolidge, resigned from the Cabinet in 1928 to become Chairman of the National Republican Committee. Dr. Work formerly practiced medicine and was a member of the House of Delegates of the American Medical Association for many years. He was the first speaker of the House of Delegates and was President of the Association in 1921.

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Dr. William J. Quigley (Associate), Lakewood, Ohio, has resigned as Assistant Clinical Professor of Medicine of the Rush Medical College.

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Surgeon General Hugh S. Cumming (Fellow), Washington, D. C., was one of the speakers at the fourth New York Health Conference held at the Hotels Roosevelt and Biltimore, March 14-15, under the auspices of seven different state, local and national agencies.

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Dr. Joseph C. Doane (Fellow), Philadelphia, recently addressed the Lackawanna County Medical Society at Scranton on diseases of the right upper quadrant of the abdomen.

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Dr. George R. Minot (Fellow), Professor of Medicine, Harvard University Medical School, and Director of the Thorndike Memorial Laboratory, delivered, March 7-8, the second course of the William Sidney Thayer and Susan Read Thayer Lectureship in Clinical Medicine at Johns Hopkins University School of Medicine, Baltimore. Dr. Minot's subjects were "Treatment of Pernicious Anemia" and "Treatment of Anemia Other Than Pernicious Anemia Particularly with Diet and Iron." This lectureship was endowed by a group of friends of Dr. William S. Thayer (Fellow) in 1927. Sir Humphrey Rolleston delivered the 1928 lectures.

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Dr. Ralph Kuhns (Associate), Chicago, was a speaker on the scientific program of the February 13 meeting of the Lake County Medical Society.

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Dr. Edward J. G. Beardsley (Fellow), Philadelphia, addressed the Philadelphia County Medical Society, February 20, on the medical aspects of modern professional pharmacy.

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Dr. William Engelbach (Fellow), St. Louis, addressed the Los Angeles County Medical Association, March 7, on "Diagnosis and Treatment of Endocrine Diseases."

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Dr. Preston M. Hickey (Fellow), Professor of Roentgenology, University of Michigan Medical School, was the guest of honor at the second Annual Meeting of the Indiana Roentgen Society, February 22. Dr. Hickey's subject was "Lateral Teleoroentgenography of the Chest."

Dr. George R. Minot (Fellow), Boston, resigned during March as head of the Medical Service of the Huntington Memorial Hospital for Cancer Research, and has been appointed successor of the late Dr. Francis W. Peabody at the Boston City Hospital.

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Dr. Frank Smithies (Fellow), Chicago, recently addressed the Marquette-Alger County Medical Society on gastric hemorrhage.

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Dr. George R. Maxwell (Associate), Morgantown, addressed the Fayette County Medical Society, March 7, on "Early Diagnosis of Pulmonary Tuberculosis."

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Dr. Robert A. Peets (Fellow), Colfax, addressed the Pasteur Society of Central California (San Francisco), February 27.

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Dr. William A. White (Fellow), Washington, D. C., was guest of honor at a dinner at the University Club (Baltimore), March 15. Dr. White's subject was "The Psychiatrist Looks at Crime."

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Dr. Harold W. Jones (Fellow), Philadelphia, on March 8, addressed the Lycoming County Medical Society (Williamsport) on "Blood Transfusions and Blood Dyscrasias."

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Dr. William F. Lorenz (Fellow), Madison, has been appointed Colonel of the 135th Medical Regiment of the Wisconsin National Guard.

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Dr. Maurice C. Pincoffs (Fellow), Baltimore, addressed the Baltimore City Medical Society, March 15, on "Paroxysmal Hypertension Due to Adrenal Tumor."

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Bernard L. Wyatt (Fellow), Tucson, resigned on April first as Director of the Desert Sanatorium and as President of the Board of Directors. Dr. Allen K. Krause (Fellow), Baltimore, has succeeded Dr. Wyatt as President of the Board of Directors.

Dr. Turner Z. Cason (Fellow), Jacksonville, spoke before the quarterly meeting of the Leon-Gadsden-Liberty-Wakulla-Jefferson County Medical Society, Tallahassee, on "Cardiac Disease in the Syphilitic."

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Dr. Elliott P. Joslin (Fellow), Clinical Professor of Medicine, Harvard University Medical School, addressed the Wayne County Medical Society, March 19, on "Present Thoughts on Diabetes and Their Application to Treatment."

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Dr. Charles H. Neilson (Fellow), St. Louis, spoke before the Waterloo Medical Society, January 16, on the nervous patient.

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Dr. Anthony Bassler (Fellow), New York, addressed the New York Gastro-Enterological Association, April 1, on "The Colopathies." Doctors Walter A. Bastedo (Fellow), New York; Charles Eastmond (Fellow), Brooklyn; Dr. Max Einhorn (Fellow), Nenw York; and Albert F. R. Andresen (Fellow), Brooklyn were discussants.

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One of the floors of the new Maternity Department of the Georgetown University Hospital, Washington, will bear the name of Dr. George M. Kober (Fellow), who recently retired as Dean of the Georgetown University Medical School after many years' service.

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Dr. Andrew C. Ivy (Fellow), Chicago, is Secretary of a Committee which met March 18 at the City Club of Chicago to formulate plans to oppose the antivivisection bill which was introduced, March 7, in the Illinois legislature.

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Dr. John A. Lichty (Fellow), Clifton Springs, addressed the Pinellas County Medical Society, March 8, on "Achylia Gastrica and its Significance in Relation to other Diseases," with lantern slides.

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Dr. Lawrence Litchfield (Fellow), Pittsburgh, is a member of the Publication Committee of the Pennsylvania Medical Journal. Dr. George E. Holtzapple (Fellow),

York, Dr. H. Brooker Mills (Fellow), Philadelphia, and Dr. Arthur C. Morgan (Fellow), Philadelphia, are Associate Editors of this Journal.

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Dr. Richard Hayes (Fellow), D.M.R.E. (Camb.) of Longview, Wash., addressed the Annual Convention of the Radiological Society at Chicago, December 7, 1928, on Chronic Duodenal Ileus.

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Dr. C. V. Weller of the department of pathology of the University of Michigan presented a paper on "Degrees of Entdifferentiation in Primary Carcinoma of the Lung," at the Chicago Meeting of The American Association for Cancer Research March 27. At the meeting of the American Association of Pathologists and Bacteriologists, on Friday, March 29, he read a paper on "Calcification of the Kidneys in Bismuth Poisoning."

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Dr. Aldred Scott Warthin presided at the Chicago meeting of the American Association for Cancer Research, March 27th in place of Dr. J. F. Schamberg who prevented by illness from attending. Dr. Warthin presented papers before this association and also before the American Association of Pathologists and Bacteriologists on March 28.

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## MEETING AND DINNER BY MILWAUKEE MEMBERS

The following Milwaukee members of the American College of Physicians held a meeting and were entertained at dinner at the home of Dr. Rock Sleyster, Wauwatosa, Wisconsin, on February 11: Dr. Arthur J. Patek, Dr. Louis M. Warfield, Dr. J. Gurney Taylor, Dr. R. W. Blumenthal, Dr. Oscar Lotz, Dr. Alfred W. Gray, Dr. C. H. Stoddard, all of Milwaukee, Wisconsin.

Dr. Sleyster is the member of the Board of Governors representing Wisconsin, and, therefore, sponsored the meeting. College matters in general were discussed, plans for attending the Boston Clinical Session were made and a survey of eligible candidates for Fellowship and Associateship was considered. Discussion was entered into concerning whether Dermatology and Roentgenology are properly classified as branches of Internal Medicine, and whether men practicing these specialties should be eligible for membership in the American College of Physicians. (*Editor's Note*: Both Dermatologists and Roentgenologists are at present eligible for membership, and in fact a considerable number are represented in the membership.) It was further the consensus of opinion of this group that the annual meeting would be more valuable if papers were open for discussion and someone prepared to open the same. Furthermore, the suggestion was advanced that the member of the Board of Governors for any state should be elected by the Fellows and Masters from that State, instead of by the present plan of election of all Governors at the General Business Meeting of the College.

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"Dr. J. W. Torbett, Marlin, Texas, recently delivered an address before the Central Texas District Medical Society in Temple, Texas, on the subject of "Systemic Diseases from Focal Infections of Peribronchial and Other Lymphoid Glands Following Influenza." A similar address will be delivered before the State Medical Association at Brownsville in May. Dr. Torbett was recently elected Vice-President of the American College of Physio-therapy at its meeting in Chicago and has been appointed toastmaster of the annual banquet and Chairman of the Section of Dietetics of the American Electrotherapeutic Association which meets in Indianapolis this coming September.

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Dr. Anthony Bassler (Fellow) read a paper on the "Biological Importance of the Intestinal Tract" before the West End Medical Society on March 1. And will present "Some Treatment Points on Gastroduodenal Ulcer" befor the North Bronx Medical Society on March 19, "The Colopathies" before the New York Gastroenterological Association April 1, And "The Significance of Biological Intestinal States

in the Specialism" before the Progressive Medical Society April 2. So far this Winter Dr. Bassler has presented 9 contributions on intestinal biological subjects, has addressed 27 medical organizations on gastroenterological subjects, and read papers in 11 states.

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## *OBITUARY*

Dr. Charles Lyman Greene (Fellow), Saint Paul, died January 19, 1929, of cerebral hemorrhage, aged 66 years.

Dr. Greene was born in the town of Gray, Maine, the son of a surgeon. He began the study of medicine at the University of Michigan, but later changed to the University of Minnesota College of Medicine, from which he graduated in 1890. After pursuing postgraduate study in Vienna, he was appointed first assistant city physician of Saint Paul. Later he took postgraduate work at Harvard and Johns Hopkins Universities, and became Lecturer in Applied Anatomy at the University of Minnesota, 1892-94; Professor of same 1894-97; Professor of Clinical Medicine and Physical Diagnosis same 1897-1903; Professor of Therapy and Practice same 1903-09; Professor of Medicine and Chief of the Department of Medicine and Chief of the Clinic at the University of Minnesota Hospitals, 1909-15. Dr. Greene was Chief of Staff of St. Luke's Hospital from 1925 to the time of his death, and had also been acting as Consulting Physician to the State Hospital for Crippled Children and Attending Physician to the Miller Hospital. During the World War, he was commissioned Lieutenant Colonel in the Medical Corps of the U. S. Army, and at the time of his death held the rank of Colonel in the Medical Reserve.

He was a member of his County Medical Society, ex-President of the Minnesota State Medical Association, a Fellow of the American Medical Association, a member of the American Therapeutic Society, a member of the Association of American Physicians, and a Fellow of the American College of Physicians since December 29, 1916. He was formerly Medical Director of the Minnesota Mutual Life Insurance Company and President of the National Association of Life Insurance Examiners.

Dr. Greene was well known nationally as a medical author. His articles appeared frequently in local medical journals and were published in many national journals. He was the author of a book on Medical Examination for Life Insurance, but his most important work was his Medical Diagnosis, which was published through six editions, the last appearing in 1926.

Dr. Greene's generosity and equanimity endeared him to a host of friends both within and outside the ranks of the profession.

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Dr. John Craig Taylor (Fellow), Chelsea, Oklahoma, died March 4, 1929; aged 55.

Dr. Taylor was born at Columbus, Kentucky, attended the University of Louisville and received his Medical Degree from that institution in 1898. He pursued postgraduate study at the Harvard Medical School, the Chicago Polyclinic and the Tulane University

of Louisiana. He also was a frequent visitor to the Mayo Clinic at Rochester, Minnesota, and as late as 1926, pursued organized extension courses offered by the University of Oklahoma. He was a member of the Rogers County Medical Society, the Oklahoma State Medical Association, the American Medical Association, the Medical Association of the Southwest and a Fellow of the American College of Physicians since March 4, 1928, having been elected during the Twelfth Annual Clinical Session at New Orleans.

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JOHN PHILLIPS, M.D.

The tragic death of Dr. Phillips, by gas poisoning in the Cleveland Clinic Disaster, closed one of the most brilliant careers in Cleveland Medicine. In twenty-three years he rose from resident physician at Lakeside Hospital to Assistant Professor of Medicine in Western Reserve Medical School, visiting physician to Lakeside Hospital, consulting physician to Rainbow, St. Johns and Maternity Hospitals and finally to director and chief of the Medical Division of the Cleveland Clinic. In addition, through his early association with Dr. Edward Cushing, he acquired a large private practice and retained the confidence of many of the old Cleveland families. Later as medical chief at the Clinic, he carried on an enormous consulting practice.

Dr. Phillips was greatly interested in the American College of Physicians from its beginning, and was elected to the Board of Regents in 1923. He has been very active in the affairs of the College since that time, serving on the Executive Committee, on the Committee on Constitution and By-Laws, and as chairman of the Committee on Postgraduate Medical Instruction. He was the local Chairman of Arrangements for the Annual Session in Cleveland in 1927.

Dr. Phillips was born in Welland, Ontario, in 1879, and had his early training in the public schools and at the Model Teachers Training School of Welland. He received his M.B. degree from the University of Toronto in 1903. Following this he served as interne and resident physician at Lakeside Hospital, Cleveland, until 1906. During this period his ability, extraordinary industry, working capacity, and hard practical common sense attracted the attention of Dr. Cushing, then visiting physician at Lakeside, and led to the association which formed the basis of his career. He also did postgraduate work at Johns Hopkins Hospital. In his early years of practice he paid especial attention to pediatrics, and became attending physician to the Babies Dispensary and Hospital. He never lost his interest in this field. He later became an active member of the American Child Hygiene Association, also of the American Heart Association, the Association for Study of Internal Secretions, the American Gastro-enterological Association and other national organizations.

The most outstanding characteristics of Dr. Phillips' personality were simplicity, directness, poise and a remarkable sense of relative values. He drew conclusions rapidly and used his own experience very effectively in the direction of progressive growth. Although possessed of a high degree of mental acumen and a remarkable memory he

regarded long, continuous, hard work as the main road to success. Work was his philosophy of life; he practically never played. Medical activities of some kind seemed to satisfy all his recreational needs. He was always optimistic, constructive and helpful. Although never fond of writing, he so disciplined himself in all necessary phases of medical life that he published over fifty articles in various journals, a section on "Diseases of the Pleura" in "Cecil's Medical System" and just before his death delivered his manuscript on "Diseases of the Gall Bladder and Liver" for a series of monographs to be published in book form by Dr. Henry Christian.

Although never attracted to military life, Dr. Phillips accepted the call of service in 1918 and became captain in the Medical Corps of the Army at Camp Jackson in South Carolina and consultant in charge of the cardiovascular board at Camp Upton. Upon returning to civil life, the advantages of group practice as observed in the army appealed to Dr. Phillips, and when the opportunity of becoming a co-developer of the Cleveland Clinic with Drs. Crile, Lower and Bunts came to him, he was thrilled with the idea of a new objective for which to work. His energy, loyalty, and ability contributed consistently to the growth of the institution. He had entire charge of the medical division.

The untimely death of Dr. Phillips is a great loss to the Cleveland profession, and to the official family of the American College of Physicians.

(Contributed by V. C. Rowland, M.D., Cleveland, Ohio)

## SHOULD THE COLLEGE CONDUCT A PLACEMENT SERVICE?

From time to time, suggestions have been received that the College should organize a Placement Service, whose object it would be to assist its members in locating able assistants, laboratory workers, technicians, etc., and also to assist members who seek new locations or connections. This would necessitate the setting up of records in the Executive Offices of lists of vacancies and lists of available candidates. The College could not, it is thought, assume any responsibility in respect to the success of candidates or the satisfaction of appointments, but it could perform that service of getting those who are seeking appointments in touch with those who have vacancies.

During recent months, the Executive Secretary has been asked to locate candidates for a number of positions, such as the following: (a) Laboratory worker with medical degree to take full charge of a laboratory in Panama City; (b) Assistant Physician to an Internist in Boise, Idaho; (c) Associate Secretary of the Public Health Federation of a city in Ohio; (d) House Surgeon for a large industrial firm near Philadelphia. Salaries in these positions varied from $3,500 to $6,000.

Members of the American College of Physicians who read this article are requested to express their opinions by letter to Mr. E. R. Loveland, Executive Secretary, 133-135 S. 36th Street, Philadelphia, Pa.

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